

Genetic characteristics of competitive swimmers: a review

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ABSTRACT: A successful swimming performance is a multi-factorial accomplishment, resulting from a complex interaction of physical, biomechanical, physiological and psychological factors, all of which are strongly affected by the special medium of water as well as by genetic factors. The nature of competitive swimming is unique, as most of the competitive events last less than four minutes. Yet training regimens have an endurance nature (many hours and many kilometres of swimming every day), which makes it impossible to classify swimming by definitions of aerobic-type or anaerobic-type events, as in track and field sports. Therefore, genetic variants associated with swimming performance are not necessarily related to metabolic pathways, but rather to blood lactate transport (*MCT1*), muscle functioning (*IGF1* axis), muscle damage (*IL6*) and others. The current paper reviews the main findings on the leading 12 genetic polymorphisms (located in the *ACE*, *ACTN3*, *AMPD1*, *BDKRB2*, *IGF1*, *IL6*, *MCT1*, *MSTN*, *NOS3*, *PPARA*, *PPARGC1A*, and *VEGFR2* genes) related to swimming performance, while taking into consideration the unique environment of this sport.

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INTRODUCTION

Swimming is one of the most popular modes of physical activity around the world, both in recreational and in sport environments [1, 2]. Furthermore, competitive swimmers continue to break world records more frequently and with greater margins than in most other sports [3, 4]. However, despite its popularity and success, swimming has received less attention in the scientific literature compared with running or cycling (464 scientific swimming papers were published on PubMed in 2015–2020 compared to 1666 papers on running). One main reason for this may be the difficulty of collecting physiological measurements during swimming. In addition, the physical properties of water, including its density, pressure, thermal capacity and conductivity, elicit distinct physiological effects on swimmers, and represent significant challenges to investigators specializing in this unique medium.

Specifically, the horizontal body position alters the gravitational effects on circulation [5]. Although cardiac output remains unchanged, stroke volume increases and heart rate decreases compared to running for a given oxygen uptake level [6–8]. Local factors, such as peripheral circulation, capillary density, perfusion pressure and metabolic capacity of active muscles, are important determinants of the power production capacity and emphasize the role of swimming-specific training movements [9]. Breathing in

swimming is restricted by stroke mechanics and the aquatic environment. The limitations on the respiratory, central circulatory or peripheral/muscular capacities for oxygen transport and utilization usually induce a reduction of about 10% in maximal oxygen uptake compared to running [10]. Thermoregulatory demands do not compete with metabolic demands during high-intensity swimming at temperatures that normally exist during training and competition [11].

Research on competitive swimming has given special emphasis to energetic and biomechanical assessments [12, 13]. It is well established that the energy expended to transport the body over a given distance increases with speed, both in water [14, 15] and in land activities such as running [16] or cycling [17]. However, at any given speed, the cost of energy is lower on land than in water [18]. This is because of the need to overcome larger resistance forces in the water (hydrodynamic resistance) than on land (aerodynamic resistance) [19]. In addition, there is a lower propelling efficiency in the water compared to on land (e.g., a lower capability to exert useful forces in water than on land) [18]. This also explains the reasons why there are differences in the energy cost of the different strokes (the energy expenditure for a given swimming speed is lowest in the front crawl, followed by the backstroke, butterfly and breaststroke)

or in swimmers with different technical skills [20, 21]. This is also why the swimmers' skill in reducing water resistance, as well as in applying propulsive forces effectively, may be more important in dictating the physiological and energetic demands of swimming than a simple kinematic analysis of race duration [22, 23].

As can be learned from the literature, performance in swimming is strongly linked to energetic variables, as these are dependent on the swimmers' biomechanical profile and on motor strategies adopted by the swimmers [24]. Consistent with this is the strong correlation that was found between the 100 m and 2000 m swim times of elite male swimmers specializing in 100 to 800 m distances [25]. Such a correlation may indicate that factors such as the swimmers' technique, body size (particularly limb length) and swimming motor strategies are major determinants of the swimmers' level [26, 27]. It is therefore likely that these variables, at least partially, mask metabolic differences between swimmers of different specialties, enabling technically skilled and tall swimmers to excel at all swimming events [28, 29]. This assumption can be supported by past records of top world-class swimmers, such as Ian Thorpe (world record holder in the 200, 400 and 800 m) and Grant Hackett (world record holder in the 400, 800 and 1500 m). While strong relationships between sprint and long-distance results are characteristic for swimming, they are very uncommon in running events.

Performance in competitive swimming is the result of a complex interaction of physical, biomechanical, physiological and psychological factors, all of which are strongly affected by the special medium of water [26,28,30]. It should be noted, however, that most competitive events in swimming last less than four minutes. Yet, by tradition, elite swimmers spend many hours and many kilometres of swimming in training every day [31]. It is doubtful whether the high volume of work among these swimmers is really necessary to improve swimming records. Although research on swimming has given emphasis to biomechanical and energetics assessment to understand the special needs of swimming, in the last few years special attention has been given to studying the genetic characteristics of swimmers.

The primary aim of the current review is to outline the main genetic predictors of competitive swimming performance. This research work was designed as an overview of the scientific literature. General recommendations to improve the quality of narrative reviews were taken into account for better structuring this research [32,33]. Scientific databases such as Medline, ScienceDirect, SPORTDiscus and Google Scholar were searched for articles on the topic with relevant keywords, including "genetic*", "*polymorphism*", "*swimming*".

RESULTS

Identification of genes that promote athletic excellence is challenging, mainly because the contribution of each possible gene to the overall heritability is small [31, 34]. Thus, the potential use of single nucleotide polymorphism (SNP) as a tool to assist in the prediction of future athletic success is still theoretical.

Efforts to use genetics for sports selection and prediction of sports excellence are particularly relevant in young ages [35]. Children are encouraged to participate in sports at a level consistent with their abilities [36, 37]. Thus, directing children to exercise at or above their limits, or to specialize in a single sport before adolescence, is discouraged [38]. Despite this, an increasing number of children do specialize in a sport such as swimming at an early age, and compete at an "elite" level [39, 40]. Moreover, some Olympic sports have selection processes that attempt to identify future champions and initiate specialized training, even before elementary school [41]. In addition, media coverage of sports often focuses on very talented but very young competitors [42]. Even more complex is a situation where sports-talented pre-pubertal children often excel in aerobic, anaerobic, individual, as well as team sports [43]. Thus, it seems that a key factor for competitive sports success is identification of a sport event that best matches the athlete's ability at an appropriate age [36, 44, 45]. Genetic polymorphism may be used as an additional scientific tool to assist athletes and coaches in sport selection [35]. Yet, it should be noted that although a favourable genetic profile is necessary for athletic excellence, other factors including advanced training methods, equipment and facilities; adequate nutrition; psychological health; high motivation; and familial support are also crucial for top-level excellence in sports. While sports genetics research has focused mainly on individual sports, the majority of these studies examined runners and cyclists, and studies on the genetic characteristics of swimming have emerged only in recent years with the work of Woods *et al.* in 2001 [46].

DISCUSSION

ACE related genes

The renin-angiotensin system (RAS) plays a key role in human circulatory homeostasis. One of the main components of the RAS is angiotensin-converting enzyme (ACE), which catalyses production of angiotensin II (ANG II) from angiotensin I (ANG I), consequently increasing blood pressure. Furthermore, ACE is an essential part of the kallikrein-kinin system (KKS), where it degrades kinins into inactive fragments, thus reducing blood pressure [47, 48].

ACE

The human angiotensin converting enzyme gene (*ACE*) is located on chromosome 17 in position 17q23.3[49]. The enzyme coded by this gene converts angiotensin I to II and is a key element in the renin angiotensin system (RAS), a system responsible for the regulation of blood pressure. The most widely studied *ACE* polymorphism is the restriction fragment length polymorphism consisting of the insertion (I) or deletion (D) of a 287 base pair repeat sequence in intron 16 (rs4340). The I allele is associated with lower ACE activity in both serum and tissue compared with the D allele [50].

D allele carriers have shown greater strength gains and muscle volume after isometric strength training in quadriceps muscles [51]. The I allele was associated with endurance performance [51],

greater improvements in medium duration aerobic performance [52] as well as with an increase in the proportion of free fibres (type I muscle fibres) [53]. Nevertheless, some studies do not confirm these observations [54].

Some studies [55–57] but not all [58] have shown that the I allele is more prevalent among long distance swimmers compared to controls. However, I allele prevalence was similar among short- and long-distance swimmers [56] indicating that this polymorphism cannot distinguish between the two specialties.

BDKRB2

Bradykinin (BK) is a vasodilator, released from kininogens [59, 60]. BK is involved in various biological processes and its action is mainly mediated by one of its two receptors, the bradykinin 2 receptor (BDKRB2) [61]. The receptors are located on the plasma membrane of skeletal muscle cells and the vascular endothelium [48]. The activation of BDKRB2 results in increased skeletal muscle glucose uptake during physical activity, increase of muscle blood flow, and as a result higher endurance performance [47].

BDKRB2 is encoded by the *BDKRB2* gene, located on chromosome 14q32 and expressed in most human tissues. An insertion/deletion polymorphism of 9 base pairs (bp) (-9/+9, rs5810761) in exon 1 is the most frequently investigated polymorphism in the context of relationships between genotypes and athletic status [47]. The -9bp allele is associated with higher gene transcriptional activity, higher mRNA expression, and increased receptor activity [62, 63]. As a result, the -9 allele may be connected with higher skeletal muscle metabolic efficiency and endurance performance [47]. Indeed, The *BDKRB2* -9 allele was found to be associated with endurance performance [47, 48, 64–66]. Specifically, The *BDKRB2* -9 allele was over-represented in long-distance (800–1500 m) swimmers compared to controls (72.2 vs 45.9%; $P = 0.032$) [64]. The +9 allele was over-represented in short-distance (50–100 m) swimmers compared to controls (67.9 vs 54.1%; $P = 0.044$) [64], and the +9/+9 *BDKRB2* genotype was associated with a greater improvement in swimming performance in response to training [68]. However, in another study, Grenda et. al [67] statistically significant differences in *BDKRB2* genotype and allele frequencies between long-distance swimmers and the total group of swimmers or controls, meaning that the *BDKRB2* -9/+9 polymorphism was not associated with swimming performance at short, middle or long distance, regardless of gender among Polish swimmers.

AMPD1

Adenosine monophosphate deaminase (AMPD) is a very important regulator of muscle energy metabolism during exercise [68–70]. AMPD plays a pivotal role in ATP production through converting AMP to inosine monophosphate (IMP) [68–72] as well as in glycolytic pathway regulation [68, 71, 72]. AMPD expression in skeletal muscle is dependent on muscle fibre composition [68, 70–72]. A decrease in AMPD activity was reported concurrent with an increase in the

proportion of fast-twitch (type II) fibres affecting, therefore, intense anaerobic physical activity [73–75].

The gene encoding the isoform (*AMPD1*) is located on chromosome 1 (1p13). *AMPD1* is mainly expressed in fast-twitch (type II) muscle fibres. Differential *AMPD1* gene expression may contribute to quantitative variations in enzyme activity across muscle groups with different types of fibres [71, 72, 75]. The nonsense mutation c.34C > T (rs17602729) in exon 2 of the *AMPD1* gene converts glutamine codon (CAA) into the premature stop codon (TAA), which results in the early interruption of protein synthesis and appears to be the main cause of AMPD deficiency [76].

TT carriers have extremely low skeletal muscle AMPD activity compared to CT and CC carriers [71, 75]. T allele prevalence is lower among elite endurance athletes compared to controls [70, 77, 78]. A significant deficiency of the T allele was noted among short-distance swimmers compared to controls [79] suggesting, that short-distance swimming requires endurance abilities.

NOS3

Nitric oxide (NO) is a gaseous free radical synthesized from arginine by the nitric oxide synthase (NOS) enzymes. Both neuronal NOS (nNOS, NOS1) and endothelial NOS (eNOS, NOS3) are constitutively expressed, while inducible NOS (iNOS, NOS2) is not expressed under normal circumstance, but may be induced under stress conditions [80]. NO is involved in various aspects of skeletal muscle structure and function [81], all crucial for aerobic and anaerobic performance [82, 83]. Two NOS isoforms were identified in skeletal muscles – nNOS and eNOS. nNOS is the primary skeletal muscle isoform, whereas eNOS is expressed mainly in endothelial cells and contributes mostly to vascular tone control. Endothelial nitric oxide synthase (eNOS or NOS3) is encoded by *NOS3* gene that is located on chromosome 7 (7q36) [84, 85]. Several investigations have demonstrated that *NOS3* polymorphic variants can lead to altered transcription and/or processing rates of eNOS, and as a result interfere with normal enzyme function [86]. *NOS3* gene – polymorphisms are associated with several health/fitness, exercise and training response phenotypes [87]. The -786T/C (rs2070744) and G894T(rs1799983) variants of *NOS3* have been associated with endurance performance among elite endurance athletes [66, 88], power athletes [89, 90] and soccer players [91], as well as with the differentiation of elite power from endurance athletes [92]. Recently it was found that the -786T allele and the G-T haplotype of the -786T/C and G894T polymorphisms may be beneficial for long-distance swimming [93].

PPAR genes

Peroxisome proliferator activated receptor-alpha (PPAR-a) and peroxisome proliferator activated receptor gamma coactivator 1 alpha (PPARGC1A) play an important role in muscle fibre type conversion [94, 95]. PPARs are transcriptional factors which, through stimulation, affect glucose and fat metabolism [96], inflammatory

processes [97], division and differentiation of some cell types [98] and energy homeostasis [99, 100].

The *PPARA* gene is located on chromosome 22 (22q12–q13.1 [101]). The most frequently analysed genetic variant in this gene is a polymorphism located in intron 7 (G/C, rs4253778). The *PPARA* gene is activated under conditions of energy deprivation, promoting uptake, utilization, and catabolism of fatty acids [102]. There is evidence that this gene is involved in the immune responses of the human body to endurance training, as it enables activation of the FAO mitochondrial pathway [97]. The *PPARA* gene is expressed at high levels in tissues that catabolize fatty acids, such as the liver, skeletal muscle, and heart [103]. There are findings indicating that *PPARA* gene G/C polymorphism is associated with swimming performance. The G allele was over-represented in LDS compared to controls (95.8 vs 83.6%; $P = 0.023$), while the C allele was over-represented in SDS compared to controls (33.8 vs 16.4%; $P = 0.0002$) [104]. A meta-analysis on 760 endurance athletes, including swimmers, and 1792 controls, found higher frequency of the GG genotype and G allele among athletes compared to controls [105]. No association was found between *PPARA* G/C polymorphism and performance among power-type Ukrainian athletes, including short-distance swimmers [106].

PPARGC1A has been suggested to affect athletic performance because of its role in a wide variety of biological responses [107, 108]. It encodes peroxisome proliferator-activated receptor γ coactivator 1 α (PGC1 α), a transcriptional coactivator of the peroxisome proliferator-activated receptor (PPAR) family. PGC1 α regulates the expression of several key genes involved in glucose and fatty acid oxidation [109, 110]. It is also a key stimulator of mitochondrial biogenesis by activating transcription of the nuclear respiratory factors NRF1 and NRF2, inducing expression of mitochondrial transcription factor A (TFAM)[111]. PGC1 α is also important for skeletal muscle fibre conversion. Over-expression of *PPARGC1A* leads to the conversion of fast-twitch type IIb muscle fibres to type IIa and slow-twitch type I fibres [112]. Furthermore, *PPARGC1A* expression correlates with both short-term exercise and endurance training in rodents and humans [113–115].

The *PPARGC1A* gene is located on chromosome 4 (4p15.2). The Gly482Ser (rs8192678) gene polymorphism is the most frequently analysed. This polymorphism was reported to be associated with type 2 diabetes, obesity and elevated blood pressure [116–118]. The 482Ser allele was under-represented in the cohort of Polish and Russian athletes examined compared to nonathletic controls. A significantly low frequency of the 482Ser allele was observed among the endurance, strength-endurance, and sprint-strength groups of Polish athletes (which include long-, middle- and short-distance swimmers respectively), and was also less prevalent in groups of Russian endurance and strength-endurance athletes (which include long- and short-distance swimmers respectively). The authors concluded that the *PPARGC1A* Gly482 allele may be considered a beneficial factor for endurance performance [119]. A meta-analysis on

1,979 endurance athletes (including long-distance swimmers) and 1729 power type athletes (including short-distance swimmers) revealed that the Gly/Gly genotype and the Gly allele of the *PPARGC1A* Gly482Ser polymorphism may facilitate athletic performance regardless of the type of sport [120].

VEGFR2

Vascular endothelial growth factor (VEGF) is a major growth peptide regulating skeletal muscle angiogenesis [121]. VEGF is associated with proportion of oxidative skeletal muscle fibres (type I) and maximal rate of oxygen consumption [122, 123]. VEGF acts via two major receptors, VEGF1 and VEGFR2, localized mostly in the vascular endothelium [121].

The *VEGFR2* gene is located on chromosome 4q11–q12. The rs1870377 T/A functional polymorphism in exon 11 results in the replacement of histidine (His) with glutamine (Gln) at the receptor within the extracellular region, which is important for ligand binding [124]. The frequency of the *VEGFR2* 472Gln allele was significantly higher in long, middle and short distance swimmers compared to controls [125]. In another study, Eider *et al.* [126] found that while the *VEGFR2* gene Gln/Gln genotype was associated with endurance performance among Polish endurance athletes, including long-distance swimmers, when long-distance swimmers were separated from other endurance-type sports, no statistically significant difference between swimmers and controls was found.

Actinin-3 (ACTN3) gene

The human *ACTN3* gene encodes α -actinin-3, an actin-binding protein with a structural role at the sarcomeric Z-line in glycolytic (type II, fast-twitch) muscle fibres, and plays an important role in muscle metabolism regulation [127]. A common genetic SNP at codon 577 of *ACTN3* (rs1815739) results in the replacement of arginine (R) with a stop codon (X) [128]. The R allele is the normal functional version of the gene, whereas the X allele contains a sequence change that completely stops production of a functional protein [128]. Therefore, *ACTN3* knockout (KO) mouse exhibit reduced muscle mass, mainly due to the decreased diameter of fast muscle fibres, significant decrease in grip strength, higher endurance and a shift towards increased activity of the mitochondrial oxidative metabolism compared with wild-type mice [129, 130].

A significant association between the *ACTN3* genotype and athletic performance was first demonstrated by Yang *et al.* [131]. They showed that both male and female elite sprinters have significantly higher frequencies of the 577R allele compared to controls. Since then, *ACTN3* R577X has been studied in other cohorts such as rowers [132], soccer players [133], ironman triathletes [134], basketball [135] *et cetera*. Some articles have reported a strong association between the RR genotype and elite power performance [136–139]. While *ACTN3* R carriage may enhance power performance, other studies have shown that *ACTN3* XX might contribute to endurance performance [129, 130], suggesting that *ACTN3* is a bipotent gene

(carrying the R allele enhances power performance and carrying the X allele favours endurance capacity). In contrast, reports on Asian and African runners suggested that *ACTN3* deficiency was not associated with endurance performance [140, 141]. A meta-analysis of 88 articles did not confirm an association between *ACTN3* RR genotype and performance (OR, 1.03; 95% CI, 0.92–1.15). However, when the analysis was restricted to power events (sprinters and jumpers in track and field and sprinters in swimming), a significant association was found (odds ratio (OR), 1.21; 95% CI, 1.03–1.42) [142]. Overall, association studies show that the *ACTN3* R577X polymorphism plays a pivotal role in power athletic performance across multiple cohorts [143].

Interestingly, while the *ACTN3* R577X polymorphism has been studied extensively among track and field athletes (especially runners), its contributions to performance in swimming – a sport that also relies on muscle strength [144] has received little attention. A significant association between the *ACTN3* R577X polymorphism and swimming performance was not found among Caucasian, East Asians [145] or Spanish swimmers [146]. Among Taiwanese, R allele frequency was significantly higher in female sprint swimmers of international level compared to national-level swimmers or the general population [136].

In addition, it was shown previously that the *ACTN3* R577X polymorphism was able to distinguish significantly between short- and long-distance runners, but was unable to differentiate between short- and long-distance swimmers [147]. Consistent with this, a strong correlation was found between 100 m and 2000 m swim times of elite short- and long-distance male swimmers [25]. Interestingly, both short- and long-distance swimmers had a higher RR genotype frequency compared to non-athletic controls. This implies that both short- and long-distance swimmers may benefit from *ACTN3* R allele existence, strengthening the notion that there are no clear *ACTN3* polymorphism differences between short-distance (power) and long-distance (endurance) swimmers [147]. Moreover, RR genotype and R allele frequencies (again, associated with power performance) were significantly higher among long-distance swimmers compared to long-distance runners. This may be explained by the large differences in the specific activity duration between competitive swimming and running events. The longest Olympic swimming event (1500 m ~ 15 min duration) is much shorter than the longest Olympic running race (marathon ~ 2:10 hr. duration), and therefore *ACTN3* power characteristics are needed among long-distance swimmers but much less among long-distance runners. When comparing the short duration events, there is also a large difference in the specific activity duration of competitive swimming and running events. The time of the 100 m distance covered in swimming is approximately 50 s, while the same distance covered in running takes approximately 10 s. As a result, the sprint runner relies mostly on anaerobic energy sources, while the sprint swimmer also relies on aerobic energy production for his/her activity. Therefore, short- and long-distance swimmers share some common features, and the *ACTN3* RR

genotype may not be a suitable distinguishing genetic marker between them, as it is for runners. It is possible, however, that if open water swimmers (Olympic race – 10k) and only pure swimming sprinters (50 m) were included among the long-distance and short-distance swimmers in that study, similar R allele frequency differences would have been found between the swimmers and runners.

Lactate transport genes

Skeletal muscle is the major producer and the major user of lactate in the body. Therefore, transport of lactate across the cell membrane is of considerable importance during intense aerobic and anaerobic exercise [148, 149]. Lactate transport is mediated by a proton-linked monocarboxylate transporter (MCT1 & MCT4) [150]. Previous studies have demonstrated that MCT4 is related to lactate efflux from highly glycolytic muscle fibres, while MCT1 is associated with lactate uptake for further oxidation [150–152].

The *MCT1* A1470T single nucleotide polymorphism (rs1049434) affects lactate transport across the sarcolemma [153]. The MCT1 T-allele is related to reduced lactate transport by MCT1 [154], but its implication for athletic performance is not clearly established. To the best of our knowledge, only a single study has examined the association between the *MCT1* A1470T polymorphism and athletic performance. In a study of 323 Russian athletes and 467 non-athletic controls [155], the authors found that the frequencies of the A allele and AA genotype (defined in their study as the *MCT1* polymorphism associated with reduced lactate transport) were significantly higher in endurance-oriented rowers compared to the control group. A previous study reported a 40% reduction of the lactate transport rate in red blood cells among T allele carriers [156]. Moreover, male carriers of the T allele had lower blood lactate levels compared to carriers of the AA genotype following different circuit exercise training protocols [154].

Participation in both sprint and endurance competitive swimming events results in lactate accumulation [157]. Repeating maximal performances (when progressing from preliminaries to the semifinal and to the final stage) is often required in local and international swimming championships. Therefore, efficient transfer of lactate from the active muscles to the blood following earlier maximal effort is necessary for effective recovery and improved repeated performance [158]. Interestingly, a significantly higher frequency of the T allele among Israeli swimmers compared to Israeli runners was reported [159]. Whether this suggests that swimmers better tolerate the decreased lactate transport associated with the presence of the T allele, or whether this polymorphism displays some advantage for swimmers, is currently not clear.

We previously demonstrated [25] that mean peak blood lactate level following a swimming repeated sprint test (RST) was lower than similar exercise and recovery time periods of running or cycling RST lactate levels [160]. Along with this, blood lactate concentration was relatively low (3 mmol/l) following forty 25 m swims at a 100 m race pace in highly-trained swimmers [161]. Moreover, previous studies

have shown reduced lactate accumulation following deep-water running compared to land running [162, 163]. It was suggested that the lower lactate level following exercise in the water is related – at least partially – to smaller muscle mass recruitment during swimming compared to running, and to reduced muscle fibre contraction due to reduced weight-bearing in the water. In addition, water immersion generates hydrostatic pressure resulting in fluid shift from the muscles to the blood, facilitating effective waste clearance [164, 165]. Therefore, swimmers may benefit from enhanced blood flow caused by water immersion [166], which likely improves elimination of intramuscular metabolic elimination and enhances post-competition recovery [167]. It is possible that differences in lactate level between runners and swimmers are related to lactate transport differences due to the higher presence of the *MCT1* T allele among swimmers.

The higher frequency of the *MCT1* T-allele polymorphism among swimmers also raises the possibility of genetically determined unconscious sports self-selection [159]. Many talented young athletes with excellent power-sprint or endurance ability are exposed to a large variety of sports at initial phases of their career [36]. Carrying a polymorphism like the *MCT1* T allele may limit their capability to excel in sports characterized by high lactate accumulation (e.g., sprint and middle-distance running) [36]. Consequently, they unconsciously choose swimming as their sport specialty, due to the unique physiological settings and relatively lower lactate level during exercise in the water [36].

The IGF axis genes

The potential use of genetic SNP's 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 [168]. It is now well established that an increase in insulin-like growth factor-I (IGF1) plays a pivotal role in the functional and structural muscle adaptation to exercise [169, 170]. Therefore, most previous reports related to hormonal gene polymorphism and athletic performance in professional athletes studied variations in the *IGF1* polymorphism that affect its circulating levels [171, 172]. The polymorphism of *IGF1* promoter frequency was significantly greater in athletes (9.2%) compared to controls (2.4%), and particularly among strength (11%) athletes compared to athletes participating in team sports (7.8%) [173]. A higher frequency of the *IGF1* C1245T T/T *IGF1* promoter polymorphism (associated with higher circulating IGF levels) was demonstrated among Israeli track and field athletes (4.8%), compared to controls (non-existent) [171]. Interestingly, while T/T polymorphism carriers were both endurance and power athletes, endurance athletes were of national level, but the power athletes were top international and Olympic athletes [171] (see Fig. 1). This suggests that the *IGF1* T/T (rs35767) polymorphism is more beneficial for power sport performance at the elite level. Along these lines, an assessment of the frequency of another polymorphism of the *IGF1* gene (i.e. *IGF1* rs7136446) showed that the frequency of carrying the GG genotype was significantly greater among sprinters compared to weight lifters [174]. Altogether, this may suggest that among typical power sports, the IGF1 polymorphism is more important for speed than strength sport events. In addition, the *IGF2* (rs680) GG genotype frequency was significantly greater among sprinters compared to weight lifters [175], suggesting that carrying this *IGF2* polymorphism may also be beneficial mainly for

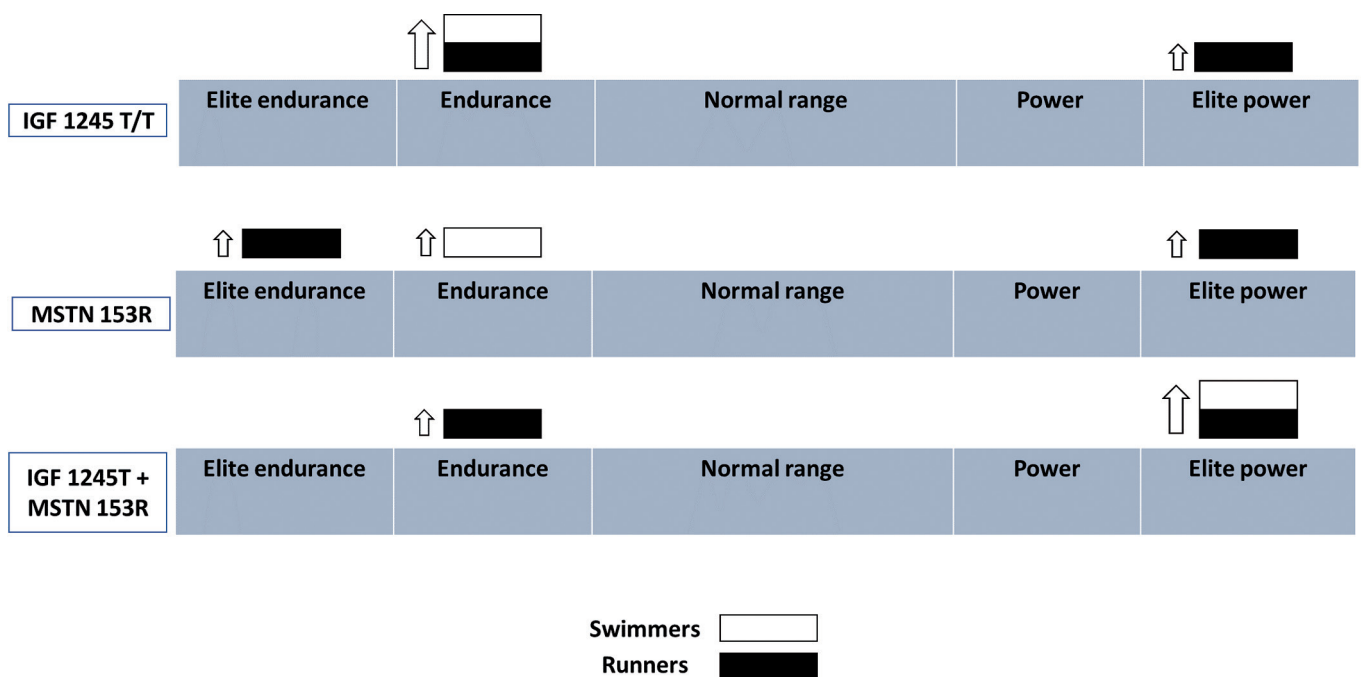


FIG. 1 IGF and myostatin gene polymorphism and competitive swimming and running.

speed-related and not for strength sports. Circulating *IGF2* levels were lower among individuals homozygous for the G allele [176], and higher levels of circulating *IGF1* levels were found in individuals carrying the *IGF2* GG genotype [177]. Thus, it is possible that the beneficial effect of the *IGF2* rs680 polymorphism on speed performance is not necessarily mediated through its influence on circulating *IGF2*, but via its effect on *IGF1* levels.

In contrast to elite track and field athletes, SNPs of *IGF1*, *IGF1* receptor and *IGF2* were not frequent among swimmers [175, 178, 179] _ENREF_74_ENREF_74. This suggests that the insulin-like growth factor system is less significant for elite swimming than for running performance, although the mechanism for this discrepancy is currently unknown. A possible explanation for this is that swimming excellence is determined primarily by the swimming technique and the swimmers' anthropometric characteristics (mainly limb length) [180], masking muscle mass and physiologic and metabolic differences, and enabling tall, long-armed and technically talented swimmers to excel in the majority of swimming distances. However, interestingly, and consistent with the findings of the *ACTN3* polymorphism [147], *IGF1* polymorphism (rs35767) frequency was also higher [171] among endurance swimmers (although not top level), emphasizing once more the importance of speed in typical long-distance swimming events.

Whether evaluation of the *IGF* axis gene polymorphism can be used for sports selection in young athletes, or whether a multi-potent athlete who wants to develop a competitive career and carries the beneficial *IGF* polymorphism should prefer track and field over swimming, is currently speculative and needs to be further studied.

Myostatin

Myostatin belongs to the transforming growth factor β super-family of proteins that control tissue growth and differentiation [181, 182]. The myostatin (*MSTN*) gene is expressed almost exclusively in skeletal-muscle cells, and functions as a negative regulator of muscle growth. [183–185] In contrast, gene knockout [186] and inhibition of the gene signalling [181] lead to dramatic muscle hypertrophy and/or hyperplasia. The *MSTN* Lys(K)-153Arg(R) polymorphism (rs1805086, 2379 A > G replacement) influences skeletal muscle phenotypes [187]. The frequency of the mutant R allele (associated with lower myostatin levels) is about 3–4% among Caucasians, with a frequency of mutant homozygote (RR) below 1% [188–190]. A previous study [191] assessed the frequency of the *MSTN* Lys(K)-153Arg(R) polymorphism among elite Israeli track and field athletes and swimmers, and found that the *MSTN* 153R allele frequency was significantly higher among top- compared to national-level runners. This suggests the possible importance of the *MSTN* K153R polymorphism for excellence in both long-distance and sprint running. Interestingly, while the frequency of the *MSTN* 153R allele was significantly greater among long-compared to short-distance swimmers, none of the long-distance swimmers who carried the *MSTN* 153RR genotype was top level. Only a single short-distance swimmer carried the *MSTN*

153R allele, indicating that this polymorphism may not be significant for success in swimming, particularly in sprints.

Since both *IGF* and myostatin regulate muscle hypertrophy, the combined frequency of the *IGF* 1245T (rs35767) and *MSTN* 153Arg(R) polymorphisms was also studied [172]. All carriers of both mutations among the short-distance runners and swimmers were of elite competitive calibre (Fig. 1).

IL6

The *IL6* -174G/C SNP modifies the *IL6* promoter activity, with carriers of the G allele demonstrating higher circulating *IL6* levels [192]. The protective effect of the *IL6* -174G genotype from developing exercise-induced muscle damage is related to greater muscle hypertrophy and improved glucose uptake, and to reduced exercise-associated muscle inflammation by favourably modifying the pro- and anti-inflammatory cytokine production balance [193–195]. In contrast, carrying the C allele (in particularly CC homozygotes), which is associated with reduced circulating *IL6* levels, increases the probability of developing eccentric exercise-related muscle injury, possibly resulting in reduced training recovery capabilities and competitive performance [196, 197]. Interestingly, a significantly higher frequency of the CC genotype was found in long-distance swimmers compared to long-distance runners and controls [198]. It was suggested that the rarity of exercise-associated rhabdomyolysis among swimmers probably results from other sport-specific and/or water-related protective factors, and is not related to genetic features [198]. It was also proposed that swimming selection in gifted endurance athletes who are C-allele carriers possibly represents genetically dependent sports selection [198]. Both disciplines (long-distance running and long-distance swimming) require remarkable endurance skills [199, 200]. However, since carriers of the *IL6* -174C allele are more susceptible to developing exercise-induced muscle damage (in particularly during land activity) [196], their recovery capabilities from intense training may be impaired. This may highlight the possibility that athletes with superior endurance abilities, but also with an unfavourable *IL6* -174C polymorphism, subconsciously prefer to specialize in water-type sports that would expose their genetic disadvantages to a lesser degree. *IL6* -174C represents, therefore, a genetic polymorphism that may lead to sports selection based on more effective training tolerability characteristics and not on performance qualities *per se*.

Interestingly, a recent study showed that carrying both the *IL6C* and *IGFBP3C* mutations was significantly more frequent among long- and short-distance swimmers compared to long-distance runners and sprinters [201]. What advantage could swimmers (both long- and short-distance) gain from carrying both mutations? Higher prevalence of the *IL6* -174C polymorphism increases the potential risk of exercise-induced muscle damage and delayed onset muscle soreness, even among swimmers – mainly following ground and resistance training, both taking a much greater place in elite swimming training over the last decades [202]. As stated earlier, an attenuated

TABLE 1. Swimming performance related genetic variants

Gene	Genetic polymorphism	Beneficial allele for swimming performance (compared to controls)		Reference
		SDS	LDS	
<i>ACE</i>	I/D rs4340	D	I	[56]
<i>ACTN3</i>	R/X rs1815739		R	[147] [25]
<i>AMPD1</i>	c.34C > T rs17602729	C		[79]
<i>BDKRB2</i>	-9/+9 rs581076	+9	-9	[64]
<i>IL6</i>	-174G/C rs1800795	C	C	[198]
<i>IGF1</i>	C1245T rs35767	IGF1 1245TT+MSTN	T	[172]
<i>MSTN</i>	Lys(K)-153Arg(R) rs1805086	153R	R	[171]
<i>MCT1</i>	A1470T rs104943	T	T	[154]
<i>NOS3</i>	786T/C rs2070744 G894T rs1799983		T G894—786T	[93]
<i>PPARA</i>	G/C rs4253778	C	G	[104]
<i>PPARGC1A</i>	Gly482Ser rs8192678	Gly	Gly	[119]
<i>VEGFR2</i>	His/Gln rs1870377	Gln	Gln	[126]

TABLE 2. Genotypes associated with competitive swimming.**Endurance related alleles that may be advantageous for long distance swimming**

- **ACE** rs4340 I
- **BDKRB2** rs581076 -9
- **NOS3 Combined** rs1799983 G + rs2070744 T
- **PPARA**rs4253778 G
- **PPARGC1A** rs8192678 Gly
- **VEGFR2** rs1870377 Gln

Muscle related alleles and genotypes that may be advantageous for long distance swimming

- **ACTN3** rs1815739 CC (RR)
- **IGF1** rs35767 TT
- **MSTN** rs1805086 R

Endurance related alleles that may be advantageous for short distance swimming

- **ACE** rs4340 D
- **AMPD1** rs17603739 C
- **BDKRB2** rs581076 +9
- **PPARA**rs4253778 C
- **PPARGC1A** rs8192678 Gly
- **VEGFR2** rs1870377 Gln

Muscle related Alleles and Genotypes that may be advantageous for elite short distance swimming

- **Combined IGF1** rs35767 TT + **MSTN** rs1805086 R

Recovery related alleles that may be advantageous for tolerating water sports

- **IL6** rs1800795 C (post exercise muscle damage)
- **MCT1** rs1049434 T (Lactate transport)

genetically predisposed insulin-like growth factor system might also be disadvantageous for swimmers, mainly in the short distances [172]. Therefore, it is possible that carrying the *IGFBP3C* polymorphism serves as a compensation mechanism. Carriers of this polymorphism have lower circulating IGF binding protein-3 (IGFBP3) levels. Therefore, levels of free IGF1, which is the actual bioactive growth factor, increase. The hypertrophic effect of higher free IGF1 levels may assist in the repair process of exercise-associated muscle damage. Again, this possible IGF-system compensating mechanism does not operate by inducing direct changes in IGF1, but instead by indirectly modifying its binding proteins.

CONCLUSIONS

Swimming performance related genetic variants are presented in Table 1. Scientific research on the relationship between genes and competitive sports, and in particular in swimming, is still in its infancy. Currently, the possibility of using genetic assessment to advise a young athlete what type of sports he/she should select, and to predict excellence or future success in professional sports, is only hypothetical. Whether a multi-potent athlete who wants to develop a competitive career and carries a beneficial IGF system polymorphism should prefer running, or carriers of unfavourable lactate transport and IL6 polymorphism should select swimming, is speculative at

present (Table 2); any genetic counselling must be interpreted with caution. Furthermore, while a favourable genetic predisposition is important, other environmental and psychological features, such as training strategy, equipment and facilities, adequate nutrition and replacement of nutritional deficiencies, familial support, competitive characteristics and motivational issues, are also critical for top-level sports success.

Finally, a major problem in genetic research is the need for a large sample size, which in many studies is very difficult to achieve. To overcome this obstacle, some studies combine different types of sports. The results presented here indicate that despite seemingly similar metabolic characteristics, athletes from different sport disciplines may carry different genetic polymorphisms. Therefore, extreme caution should be taken before pooling different types of sports in genetic research.

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Conflict of interest statement

No potential financial conflict or any other conflict of interest is reported by the authors.

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