ATHLETIC PERFORMANCE ENHANCING ACE, ACTN3, AMPD1 GENETIC MARKERS, FITNESS CHARACTERISTICS, C-REACTIVE PROTEIN AND URIC ACID OF CRICKET, NETBALL, RUGBY AND SOCCER PLAYERS: A REVIEW

Sam Chenjerai Mugandani

Center for Biokinetics, Recreation and Sport Science,
School of Health Sciences, University of Venda, South Africa

ABSTRACT

Sports is a large industry with vibrant leagues running in many countries. Some of the most popular sports are soccer, rugby, cricket and netball. To meet the demand for better performance of athletes and sustain this growing industry, coaches and trainers have depended on the manipulation of factors such as physical and physiological parameters, nutrition, tactics, techniques and psychological factors to try and improve the performance of athletes. These have been referred to as the environmental or nurture constraints. The quest for better performance continues hence microtechnology such as accelerometers, heart rate monitors and global positioning systems are also being used to gather data to determine some of the physical and physiological demands of games. Evidence from studies with twins revealed that there are performance traits which are genetically determined. Research also shows that more than 60% of performance in sport and exercise is genetically determined. The unraveling of the human genome and advances in molecular biological studies resulted in the quest for knowledge relating to the influence of genes at the molecular level on performance in exercise and sport. The human genome project established approximately 20 000 genes in humans. To date, the gene map for performance and health-related fitness phenotypes has identified more than 200 single nucleotide polymorphisms (SNPs) associated with some performance and fitness linked traits. Among the most studied gene polymorphisms are the angiotensin converting enzyme (ACE) gene, the human α- actinin-3 (ACTN3) gene and the adenosine monophosphate deaminase (AMPD1) gene, as they relate mostly to anerobic and aerobic related activities. The use of hematological and biochemical indicators to identify injuries and exercise stress calls for exploration of association between gene polymorphisms and indicators such as C-reactive protein, uric acid and blood parameters such as red blood cells and sub-components of leukocytes.

INTRODUCTION

Sports have become a large industry with vibrant leagues running in many countries. Although the population of participants is relatively low, female sport leagues are also beginning to be taken as seriously as male leagues.

In South Africa, rugby, soccer cricket and netball are very popular sports. In 2017, it was estimated that there were 9.1 million players among the world rugby union members in 121 countries. Among these, 2.4 million were female players and 603 455 of these were from

South Africa (World Rugby, 2017). South Africa hosted the world rugby cup in 1999 and the Soccer world cup in 2010. (Molly, Chetty, 2015; World Rugby, 2017). The estimated number of people playing the game of soccer world wide as of 2006 was 265 million. (McCabe, Collins, 2018). Netball has an estimated 20 million players in 80 countries and in 2010 South Africa had half a million players in schools and 9 700 adult players (Ferreira, Spammer, 2010; Mclean, 2019).

As a result of the popularity of these sports, training demands are becoming increasingly complex and very scientific, calling for analysis and structures to meet the specific needs of each sport and player. There have been efforts to improve sport performance utilizing scientific principles. Exercise and sporting movement activities are either dynamic or static. Dynamic movements involve change in length of muscles with rhythmic joint movements and the energy metabolic processes in dynamic movements are largely aerobic (Mitchell, Haskell, Snell & Van Camp, 2005). The increasing dynamic component is rated from the estimated percent of maximal oxygen consumption (MaxO$_2$) achieved during competition, ranging from low to high, where *A.* Low is (<40% MaxO$_2$), *B.* Moderate (40% -70 MaxO$_2$) and *C.* High (>70% MaxO$_2$) (Mitchell et al., 2005). Mitchell et al., also state that there are activities on the other end of the continuum whose muscle energy metabolism is mainly anaerobic, and that they develop force with minimal or no change in muscle length or joint movement. The contraction of muscles on this anerobic side of the spectrum is also referred to as maximal voluntary contraction (MVC) and is also graded from low to high as follows; *I.* low (<20% MVC), *II.* Moderate (20-50% MVC) and *III.* High (>50% MVC) (Mitchell et al. 2005).

Cricket, netball, rugby and soccer can be classified by the above characterization. Soccer is classified as *IC*, which means that it has a low anerobic, low maximal voluntary muscle contraction with a high maximal oxygen consumption and high dynamic component, rugby is *IIB,* Cricket is *IA* and netball is *IIC* (Mitchell et al., 2005). This classification is largely physical and physiological whereas in any exercising scenario the muscles accomplish mechanical (physical) and metabolic (physiological) demands (Houweling et al., 2018). The above classification suggests that cricket is low on both its aerobic and anaerobic demands, netball has moderate anaerobic demand and high aerobic demand. On the other hand, rugby is moderate on both anaerobic and aerobic requirements. However, soccer like netball has a high aerobic component but low anaerobic component.

To satisfy the ever-increasing demand for better performance of athletes and sustain the growing industry of sport, coaches and trainers now depend on the manipulation of the physical and physiological parameters, as shown in the classification above. The physical, physiological, nutrition, tactics, technique and psychological factors are called environmental or nurture constraints (MacArthur, North, 2004; Gibson 2009; Pitsiladis et al., 2016). Family studies in human movement covering identical and dizygotic twins over and above what is mentioned above also show that genetics has a contributing factor to the phenotype of sport performance (Guth, Roth, 2013; Slizik et al., 2017). Evidently, performance in sport and physical activity is a factor of both environmental or nurture constraints and genetic or nature constraints (Puthucheary et al.,2011; Ahmetov & Fedotovska, 2015). The contribution of the genetic or nature factors to athletic status is estimated to be more than 60% while the environmental factors contribute a mere one third (De Moor et al., 2007). As a result, studies have progressed at the molecular lev-

el with the use of genotyping to identify the genes and their variants which contribute to the physical and physiological basis of human performance in sport and exercise. Through genetically profiling athletes, this knowledge would be critical and helpful towards talent identification, strengthening of the training of athletes as well as identifying risks such as susceptibility to injuries (Davids, Baker, 2007; Slizik et al., 2017). The use of genetic information for research in exercise and sport has been further facilitated and enhanced by the completion of the human genome project in 2003 and the advancement of sequencing technologies (Houweling et al., 2018).

The human genome project has shown that there are approximately 20 000 genes in humans. Gene nomenclature has been established for each known human gene in the form of an approved gene name and symbol (short form abbreviation). Each symbol is unique, and each gene is only given one approved gene symbol (Carninci, Hayashizaki, 2007). Using information from the human genome project, scientists in sport science have investigated the association or linkages of genes and performance as well as health related and fitness phenotypes. This resulted in the compilation of the human gene map for performance and health- related fitness phenotypes and 120 DNA polymorphisms related to sports genomics had been identified by December 2014 (Ahmetov, Fedotovskaya, 2015). Polymorphism as a form of gene variation occurs when two or more alleles exist in a population and is related to biodiversity. Alleles are one or two alternatives of the gene that occupy the same locus (place) on a chromosome. The data available for physical performance phenotypes from the genes studied are: cardio respiratory endurance, elite endurance athletes' status, muscle strength, speed and power together with some muscle performance traits including exercise

intolerance of differing degrees (Bray et al., 2009; Ahmetov, Fedotovskaya, 2015). Energy systems, considered in the association studies, fit with the sport classification presented above. Sport teams such as cricket, netball, rugby and soccer variously fit as already illustrated (Mitchell et al., 2005).

Study approaches which are followed with gene markers are mostly case-control studies where mostly elite athletes (case) are compared to the general populations of non-athletic individuals (control) and cross-sectional studies where athletes and the general population are measured quantitatively (Ahmetov, Fedotovskaya, 2015; Houweling et al., 2018). Biomarkers are characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention (IOM (Institute of medicine), 2011). There are several biomarkers which are variously linked to physical performance and gene polymorphisms among which are C-reactive protein and uric acid. Allgrove et al., (2012) observe that exercise of elevated intensity compromises the immune system leaving athletes susceptible to illness. Therefore, hematological parameters such as leucocytes have been used as possible markers of a compromised immune system due to exercise (Mackinnon 1997; Gleeson, Walsh 2012). In this regard, soccer and rugby players have regular aerobic and anaerobic training regimes which expose them to oxidative stress (Yamaner, 2010).

METHOD
Data sources
Four hundred and fifty (450) searches were conducted and the following key words were used: ACE, ACTN3, AMPD1 polymorphisms; athletic performance; exercise, fitness and performance genomics; endurance and resistance training; Uric acid and C-Reactive protein

biomarkers in rugby, soccer and netball. Key-word searches identified articles from Medline (1987-), Research databases: Science direct (2009-), Human Kinetics (2002-), Human Gene Map for Performance and Health-related Fitness Phenotypes, the 2002 Update and the 2006-2007 update and Research Gate (2015-).

Inclusion criteria

The inclusion criteria for this review were a) ACE genotypes and associations with training response, aerobic endurance performance, VO_2max, long distance athletes, games (rugby, cricket, soccer, netball), high intensity activities of short duration, power output, exercise efficiency, muscle efficiency; b) ACTN3 genotype associations with anerobic performance; isometric and isokinetic muscle strength, properties of fast twitch and slow twitch muscle fibers in short distance athletes, games, Wingate test and pick power on response to strength training; c) AMPD1 genotypes and associations, anaerobic Wingate test for power, pick power output, mean power, muscle fibers distribution and overall strength; d) Associations of ACE, ACTN3 and AMPD1 genes with physical, physiological characteristics and blood parameters in various sports. The genotype frequencies of the polymorphisms included are presented in accordance with the genomic browsers of the USA, Indian and Arab populations (Bhagi et al.,2002; Al-Hinai et al., 2002; Salem, Batzer 2009).

Exclusion Criteria

Excluded were other potential performance enhancing genes associated with training responses and health-related phenotypes in endurance and power athletes which include, a) ADRB2 (adrenergic receptor beta 2 gene); b) VEGFA (vascular endothelial growth factor gene); c) BDKRB2 (bradykinin beta 2 receptor gene); d) NOS3 (nitric acid synthase 3 gene); e) PRARA (peroxisome proliferator activated receptor alfa gene) and f) PRARD (peroxisome proliferator receptor delta gene).

DISCUSSION

Performance demands cricket, rugby, netball and soccer

The discussion below further illustrates the performance demands of the four team sports which are both aerobic and anaerobic. This corresponds with the polymorphisms of the genes *ACE*, *ACTN3* and *AMPD1* which encode for either aerobic or anaerobic performance, except for *AMPD1* which only encodes for anaerobic performance.

Cricket

Modern cricketers are now exposed to greater physical and physiological demands. Heart rate can reach 190 beats/min and the predominant contribution from the anaerobic energy systems can contribute up to 60% of the total energy in multiple activities of short duration of less than 40 seconds (Noakes, Durandt, 2000). Martens (2004) identified the following demands of cricket: low to moderate aerobic capacity, moderate anaerobic capacity, moderate strength and flexibility, low to moderate endurance and moderate to high speed. Fast bowling has been linked with a mesomorphic somatotype, greater percentage of type II muscle fibers and superior phosphagenic and glycolytic metabolic pathways together with eccentric muscle strength (Stuelcken et al., 2007). A shorter stature and isokinetic knee and shoulder strength were seen to be contributory to the success of batsman (Noakes, Durant, 2000; Nunes, Coetzee, 2007).

Netball

Netball is a fast-paced contact sport (Soh et al., 2007; Chandler et al.,2014). Players must be endowed with speed to run short distances on the court. They perform repeated powerful jumps, well balanced landings, sudden chang-

es of direction and quick stops and starts which require agility (McManus, Stevenson & Finch, 2006; de Villiers, Venter, 2014). Both aerobic and anaerobic energy systems are a requirement (Soh, Husain & Soh, 2006; Soh, Husain & Soh, 2007; Terblanche, Venter, 2009). Using time motion analysis, centers (C) were found to have the highest player load while the goal keepers (GK) and the goal shooters (GS) had the least player loads (Fox et al., 2013; Bailey et al., 2017). The distances covered during matches are estimated to be 4210 meters for GS and 7984 meters for C (Chandler et al., 2014). Injuries occur mostly to ligaments of the ankle, knee, fingers, hands and wrists, (Langeveld, Coetzee & Holtzhausen, 2012; Hervert, Deakin & Sinclair, 2014).

Rugby

Rugby is a high-speed contact sport that involves aerobic and anaerobic fitness, there is a combination of both low and high intensity activities. In elite games running covers 5-8 km with speeds of 18-20 km/h. (Gabbett et al., 2007; Goh et al., 2009). Props are taller, heavier and their skin folds are thicker than other positions, their higher body mass helps them with momentum for their larger tackling role (O'Connor, 1996; Gabbett, 2006). Brower et al., 1994 showed that hookers, centers and wingers have better performance times in the 10and 40-m speed tests than props who were also slower than the back rowers and outside back positional groups, and backs showed significantly faster times than forwards. The hookers/halves and outside backs had superior VO_2max than the props positional groups with the highest figures being around 55.2 ml.kg^{-1}.min^{-1} (O'Connor, 1996).

Soccer

Soccer involves physical efforts of an intermittent nature with, walking, runs, sprints with or without the ball, jumps, sudden acceleration or deceleration (Devrnja & Matkovic, 2018). Soccer players should have very high speed, power, strength and endurance (Gabbett, Wiig & Spencer, 2013; O'Reilley, Wong, 2012). During a normal game, they run a total of about 10 km and within that endurance context, there are anaerobic explosive bursts, such as sprinting, jumping and forceful contractions. Thus, within an aerobic endurance context, there are numerous anaerobic explosive bursts of activity (Stølen et al., 2005; Abbey, Rankin, 2011; Calahorro et al.,2013). The average VO_2max for elite male players is between 55 and 68 ml.kg^{-1}.min^{-1}, with individual values of more than 70ml.kg^{-1}.min^{-1}(Hoff, 2005). Aerobic endurance is therefore of paramount importance (Bradley, Noakes, 2013; Sarmento et al., 2014; Varley et al., 2016). Soccer is also known to have eccentric movements such as running backwards, sudden direction changes and tackles, which lead to muscle damage (Magalhães et al.,2010; Gravina et al., 2011).

The *ACE gene*

The *ACE gene* is made up of 26 exons and 25 introns. Exons are coding sequences of DNA in the gene and introns are intragenic sequence/regions inside the gene. It stretches over 21 kilo bases on the chromosome 17q23. Its polymorphism consists of the presence of the (490bp *I* allele) or absence (190bp *D* allele) of a 287-base pair *Alu* repeat sequence resulting in three genotypes (*DD* and *II* homozygotes, and *ID* heterozygote) (Lin et al., 2001; Sipahi et al., 2006). The *I* allele refers to the presence of a 287 base *Alu* repeat segment in intron 16, the deletion or *D* is not likely to be the result of an actual deletion event. The presence of the intron 16 *Alu* on *ACE* expression is that of lowering activity levels of the ACE enzyme for individuals with the I allele.

Angiotensin converting enzyme (ACE) is

part of the rennin-angiotensin-aldosterone-system (RAAS). Renin converts angiotensinogen, to angiotensin I a peptide which is in turn converted by ACE to angiotensin II vasoactive peptide. Angiotensin II is the key agent of the RAAS. It mediates vascular resistance by binding to endothelial receptors causing vasoconstriction. ACE is a key enzyme in the generation of angiotensin, a potent vasoconstrictor as well as effector of sympathetic tone, and aldosterone stimulating peptide. Angiotensin also regulates salt and water balance via the aldosterone pathway. Its action also differs among individuals due to genetic differences (Gomez-Gallego et al., 2009). Several studies have examined the effects of *ACE* on physical performance such as aerobic capacity, muscle function, trainability, and athletic status (Scanavini et al., 2002; Lucia et al., 2005; Amir et al., 2007).

The *ACE* insertion (*ACE I*) allele is prevalent in endurance athletes hence related with endurance ability (Nazarov *et al.*, 2001). Despite research being generally inconsistent, the widely held view is that the insertion (I) allele is associated with improved performance in endurance events whereas the "deletion" (D) allele is associated with better performance in power events. However, it is not known how lower circulating ACE happens to improve performance (Wang et al., 2008). Nonetheless, it can be inferred that lower ACE in circulation could mean less conversion of angiotensin I to angiotensin II and therefore reduced vasoconstriction of blood vessels during endurance activities. The I allele is theoretically associated with a decrease in circulating levels of angiotensin II (a potent vasoconstrictor) and thus a reduction in vascular resistance which might facilitate higher cardiac output during strenuous exercise. There is an unrestricted flow of oxygen and metabolic substrates necessary for the aerobic pathways for energy production

in the skeletal muscles and other peripheral apparatus key to aerobic and 'cardiovascular' endurance. That would also explain the greater response to training in both the skeletal muscle and cardiovascular systems (Lucía *et al*., 2010). Athletes with the II genotype have greater aortic elasticity than the DD and ID genotypes (Tanriverdi et al., 2005). The I allele has also been associated with fatigue resistance in skeletal muscle (Montgomery et al., 1999). Greater percentage of the more aerobic type I skeletal muscle fibers have been found in athletes of the II genotype as compared to DD genotypes (Zhang et al., 2003). On the other hand, studies with Italian gymnasts showed the DD genotypes exhibiting higher relative strength than the II, (Calo,Vona, 2008). Similarly, a study with Caucasian Turkish female athletes showed better performance improvement in endurance with those of II genotype while those with the DD genotype improved more in the shorter more power inclined events (Cam et al., 2007). In a study of 50 to 70-year-old women the response to a 12-week varied training program showed that the ACE DD and ID did not show improvement from base line measurements in a sit to stand lower body strength test and aerobic test measured by a six-minute walk test respectively. They however showed improvements together with the II genotype group in an agility test and strength upper body arm curl test (Moraes et al., 2018). The results show some inconsistence with expected results, especially where DD would have shown association with both upper and lower strength and II not showing association with agility. In an ACE I/D variant case control study of Polish soccer players and controls, 106 players were divided into forwards, midfielders, defenders and goal keepers and there were 115 controls. Genotype and allele frequencies were not significantly different among the play positions of players neither were there

differences between the athletes and controls (Cięszczyk et al., 2016). In a similar study with 375 Brazilian soccer players of whom 90 where professionals and the other players formed strata of under 14, 15, 17 and 20 years of age, with 100 controls, the genotypic and allelic frequencies of the players in the different categories did not differ significantly from the controls (Coelho et al., 2016).

ACTN3 gene

In humans, there are two genes encoding skeletal α- actinin: ACTN2 and ACTN3 both for the structural Z discs (Bell et al., 2012). The human α- actinin-3 (ACTN3) gene encodes the structural protein α- actinin-3 in fast skeletal muscle fibers. It is located on the long arm of chromosome 11 (11q13-q14). A common polymorphism of the ACTN3 gene, 577X is due to a premature stop codon which results in a loss of function nonsense mutation. The replacement of nucleotide C (Cytosine) with T (Thymine) in exon 16 the normal codon (triplet) for Arginine (CGA) 577R is converted to the stop codon (TGA) 577X. This results in non-synthesis of the protein α- actinin-3 (North et al.,1999; MacArthur, North, 2007; Moran et al., 2007). This allele (577X) is not capable of encoding for α- actinin-3, however the presence of ACTN2 proteins in both type I and type II muscle fibers compensates for the absence of α- actinin-3 in individuals who are 577X homozygous (Calo, Vona, 2008). There are two alleles R and X, and three possible genotypes for the ACTN3 gene, which are the RR and XX homozygotes and the RX heterozygote.

The actinins (encoded by the R allele) are a group of ancient actin-binding proteins. They are limited to fast muscle fibers (type IIb) capable of generating force at high velocity (Mills et al., 2001; Vincent et al., 2007). They make up the predominant protein component

of the Z line in the type IIb muscle sarcomere to form a structure that anchors together actinin myofibrils and stabilizes the muscle contractile apparatus (Squire, 1997). They also interact with other muscle proteins in carrying out some signaling and metabolic functions (MacArthur, North, 2007). The frequency of the 577X null allele differs among different human groups. It is approximately 10% among Africans and about 18% in Caucasian populations (MacArthur et al., 2007; Norman et al., 2009). Its persistence over evolutionary time has been hypothesized to suggest that there was need to have a muscle type which would be efficient in conserving energy and resist fatigue (Calo, Vona, 2008; Head et al., 2015).

Several studies have shown substantial evidence pointing to the association of ACTN3 with physical performance. The presence of the ACTN3 protein (577R) has been shown to favor success in activities of sprint or power performance (Macarthur, North, 2005; Calo, Vona, 2008). For example, in a study of 992 Greek adolescents, male carriers of the XX genotype recorded slower sprint times compared to their RR counterparts, though this was not true for the females (Moran et al., 2007). In another study of both men and women, examining knee extensor concentric peak power, at base line, the XX carriers showed greater strength but after a 10-week training, the RR showed greater improvement compared to both the XX and RX carriers (Delmonico et al., 2007). However, in a study of East and West African athletes, there were no significant differences between sprinters of Nigerian origin with controls and the whole group showed a very low X-allele frequency. Similar results were realized with elite Jamaican and US sprinters who classified themselves as at least 50% African American. Japanese sprinters also showed better performance by RR+RX genotypes compared to ACTN3 XX genotypes (Yang et al.,

2007; Scott et al., 2009; Mikami et al., 2014). In a study of 50 to 70-year-old women, the response to a 12-week varied training program showed that the ACTN3 XX group did not show improvement in the strength sit to stand test and the RR group did not show improvement in the 6-minute walk test (Moraes et al., 2018). This is what would be expected for XX endurance genotype and RR power genotype.

In a study of 51 untrained male Caucasians, the volume of the quadriceps was measured, knee extension, one repetition maximum and maximum power were measured through pedal sprints on an isokinetic cycle ergometer. It was established that the RR genotype was superior to the XX genotype in all the three parameters (Erskine et al., 2014). To enhance the power of association, studies which have been largely limited by small numbers, 550 best times of 346 elite Caucasian sprint athletes were collected for 100m, 200m and 400m. On average, these established that athletes with the ACTN3 577RR or the ACE DD genotype had superior best times than their ACTN3 XX and ACEII counterparts (Papadimitriou et al., 2016). However, in six studies with soccer players, a distinct relationship could not be established for sprint (anaerobic) or endurance (aerobic) performance (Santiago 2008; Pimenta et al., 2012; Pimenta et al., 2013; Eyon et al., 2014; Massidda, Scorcu & Calo, 2014; Coelho et al., 2016).

Adenosine monophosphate deaminase (AMPD1) gene

The gene AMPD1 encodes for the enzyme adenosine monophosphate 1 deaminase which catalyzes the deamination of adenosine monophosphate (AMP) to inosine monophosphate (IMP) during the formation of adenosine triphosphate (ATP) in skeletal muscle and is therefore an important muscle energy regulator during exercise (Collins, 2017; McCabe, Collins 2018). The gene is in the short arm of chromosome one 1p13-p21 and consists of 16 exons and 15 introns. A nonsense mutation C to T in nucleotide 34 (C34T) in exon 2 (rs 17602729) of AMPD1 converts the codon CAA into the premature stop-codon TAA which results in the premature cessation of adenosine monophosphate deaminase synthesis. This gives rise to three variants of the gene CC, CT and TT, where CC genotype is normal and has no deficiency in the enzyme, and the presence of the T allele signals deficiency in the enzyme (Cieszczyk et al., 2011; Feng et al., 2017; McCabe, Collins, 2018).

In a case control study of Israelis consisting of endurance and sprinters competing at elite national level and a control group of non-athletic healthy individuals, the results of the study did not show any significant differences in the distribution of the three genotypes CC, CT and TT. However, the TT genotype frequency was very low in all the groups (Meckel et al., 2012). A study of Lithuanian athletes and controls showed a greater frequency of the CC genotypes among sprint anaerobic athletes, as compared to endurance, mixed athletes and controls. The TT genotype was absent in all the athletes and with only a 2.4% frequency in the non-athletic controls (Gineviciene et al., 2014). Similar results were obtained with student athletes engaged in high speed and strength sport versus students not doing any sport. The TT genotype was totally absent among athletes with a 3.8% frequency among non-athletes, with power lifting athletes registering a 100% CC genotype (Fedotovskaya, Danilova & Akhmetov, 2013). In another study, the mutation TT did not manifest at all in the Polish rowers but was present among the non-athletes at a percentage of 1.59% (Cieszczyk et al, 2011).

C-reactive protein (CRP)

CRP is a protein of the pentraxin family and is produced by hepatic cells and its production

is regulated by several cytokines including IL-1, IL-6, and TNFα which are secreted locally in the area of harmed tissue (Ablij, Meinders, 2002; Kitsios et al., 2013; Hayashino et al., 2014). It is made up of five identical subunits (protomers) each of which is capable of binding with two calcium units. The calcium allows CRP to bind with the phosphocholine ligands found in the cell membranes and plasma lipoproteins and as a result of this binding, phagocytosis of damaged cell materials and pathogens is facilitated (Ablij & Meinders, 2002; Michigan et al., 2011). The median concentration of CRP in serum is 0.8 mg/l. and this concentration can increase drastically following microbial infection, trauma and strenuous exercise by as much as 1000 times in a space of 48 hours (Heikkila et al., 2007; Jabs et al., 2005). These concentrations may remain high if exercise induced muscle damage remains in force (Gabay, Kushner, 1999). CRP is broken down in the liver, with a small proportion being taken care of by neutrophils and macrophages. The biological half-time of the removal of the protein from blood serum is 19 hours irrespective of the physiological or infection levels, and the significant determiner of the serum levels of CRP is the rate at which it is produced by hepatocytes. This makes it a suitable marker or indicator of the inflammation or disease activity in the body (Ablij, Meinders, 2002).

Several theories have been propounded to shade light on how exercise is likely to reduce inflammation. Loss of fat has been suggested as one of them where low levels of fat are said to reduce adipocytokines such as Interleukin 6 (IL-6) which stimulate the production of CRP from hepatocytes (Mora et al., 2006; Campbell et al., 2009). Twenty five percent of the systemic IL-6 is produced by adipocytes, and it is the IL-6 which is responsible for signaling the hepatocytes to secret CRP. It follows then that higher levels of body fat are likely to be associated with higher levels of CRP (Plaisance, Grandjean, 2006; Plaisance et al., 2007; Giannini et al., 2017). Some studies have shown significant weight lose together with reduction in CRP levels following physical activity or diets lowering body fat (Plaisance, Grandjean, 2006; Saghebjoo et al., 2018). Other research suggests that the increase in protein as a result of exercise also contributes to the anti -inflammatory mechanisms of exercise, probably due to antioxidant proteins from the effects of the exercise (Donges et al., 2010). Exercise generally has been shown to reduce resting levels of CRP (Mendham et al., 2011).

Aerobic based exercise programs have resulted in the reduction of CRP by various percentages. Donges et al., (2011) observed a 16.1% reduction following 10 weeks of aerobic training. Increases of up to 266% above baseline have been noted after a marathon race but returning to baseline levels by 48 hours. This has been postulated to be just a reaction to the tissue damage which is concomitant with the intense aerobic exercise. The long-term reaction is a lowered baseline level (Devrnja, Matkovic, 2018). Resistance based training programs have also been shown to reduce the levels of CRP with reductions being as much as 32% in some cases (Martins et al., 2010; Donges et al., 2011). Some studies have shown that combining aerobic endurance and resistance training yields better CRP reducing results than for example the utilization of endurance training on its own (Daray et al., 2010; Ricci et al., 2018).

As earlier indicated, C-reactive protein (CRP) is a biomarker signaling subclinical inflammation and exercise induced oxidative stress in which regular physical activity of moderate intensity has been shown to reduce CRP (Mattusch et al., 2000; Fallon, Fallon & Boston, 2001). This suggests that physical activity has anti-inflammatory

properties (Powers et al., 1999).

There are however very high increases in CRP post highly competitive games in elite sports. This inflammatory response differs from sport to sport depending on the duration of the games of the sport, the metabolic load and the nature and intensity of the activities during the games. Souglis et al., 2015 compared CRP levels 13 hours post-match between soccer, basketball, handball and volleyball players. Soccer players who, on average, cover distances of 9.5 to 10.7 kilometers per game had CRP increases of 290% from base line. They were followed by basketball and handball players (120%) who, on average, cover 4 to 4.5 km per game. The lowest increase of 80% was observed among volleyball players.

Heightened levels of CRP have also been known to increase the risk of acute myocardial infarction, ischemic stroke, peripheral artery disease, type 2 diabetes and metabolic syndrome (Hu et al., 2004).

Uric Acid

Uric acid (UA) is an endogenous antioxidant. Its levels in the body at rest are <7mg/dl in men and <6 mg/dl in women and its levels have been shown to rise in proportion to exercise intensity and training levels due to oxidative stress imposed by physical activity (Brites, 1999; Yamaner, 2010). It is recognized as one of the most significant antioxidants. It makes up the final product of purine bases (adenine and guanine) metabolism (Van Hoorenbeeck et al., 2012). Its concentration levels are related to the age, gender, body area, body weight, ethnicity and geographical position of the individual. It also constitutes 70% of the salivary antioxidant activity (Hadžović-Džuvo et al., 2011). The production of UA is stimulated by exercise and exercise increases purine oxidation. Since UA is the final product of purine

catabolism, UA concentration increases in the organism due to physical activity (Barros et al., 2012). Exercise may require the increase in the activity of adenylate cyclase acting as an additional source of energy by producing 1 ATP and 1 AMP from 2 ADP. While the ATP is used for energy, the AMP is degraded to IMP. The IMP is catabolized to hypoxanthine then xanthine, and ultimately to UA. In other words, UA is a final product of ATP degradation and increased adenine nucleotide turnover or degradation (Gailiūnienė et al., 2007; Tsalouhidou et al., 2007; Gatterer et al., 2013). This would explain why its levels rise in proportion to exercise intensity because it is a product of energy metabolism and hence an antioxidant associated with the metabolic processes of energy production during physical exercise (Svensson et al., 2002). The enzyme responsible for the conversion of xanthine to UA is xanthine oxidase and not xanthine dehydrogenase (González, et al., 2008). The antioxidant capabilities of UA are achieved by its ability to scavenge free radicals such as xanthine oxidase-free-radicals and in this way, the damage to cells by these species is minimized (Foksinski et al., 2007; Magalhães et al., 2010). UA is taken up from plasma into skeletal muscle where it reacts with reactive oxygen species in its antioxidant reactions. This is accompanied by increased formation of allantoin an oxidation product of UA in the skeletal muscles (Svensson et al., 2002). The rise in levels of UA due to exercise usually do not exceed one day and they also do not normally go above normal plasma concentration, a condition referred to as hyperuricemia (Tsalouhidou et al., 2007). Some studies have shown that chronic exercise has the effect of making the levels of UA in trained individuals higher both at rest and after exercise than in untrained non exercising individuals (Tsalouhidou et al., 2007).

Hematological acute and chronic response to exercise

Hematological parameters, just like the biochemical factors, are more sensitive indicators of responses to exercise than physical and body composition variables (Lombardi et al., 2011). Exercise stress has been known to increase leukocytes and the increase is more significant following intensive exercise. Hemoglobin and hematocrit on the other hand, will decrease, a condition known as athlete anemia and this is as a result of hemolysis and hemodilution (Kargotich et al., 2007; Suhr et al., 2009; Nazmi et al.,2014). Some studies with soccer players however have not shown a decrease in hemoglobin, hematocrit and red blood cells (Bekris et al., 2015; Santi Maria et al., 2013). This shows contradictions among various studies. In most cases, however, all the subtypes of leukocytes (neutrophils, monocytes, lymphocytes) increase during and after physical exertion (Kakanis et al., 2010; Morgado, et al., 2016). On the other hand, the number of eosinophils remains unchanged or decreases (Kakanis, et al., 2010).

A single bout of 2 hours of exercise at 75% of heart rate maximum caused leukocytosis in female soccer players mainly due to a significant rise of neutrophils (Avloniti et al., 2007). Similar results were obtained with male young soccer players and the increase in neutrophils was ascribed to the inflammatory nature of muscle damage (Devrnja & Matkovic, 2018). A significant decrease in percentage of hematocrit was observed immediately after a soccer game of under 21 soccer players, and only mean cell hemoglobin corpuscular increased significantly, with no change in the hemoglobin levels (Sporiš et al., 2016).

CONCLUSION

Performance in sport and exercise especially at elite level is made up of a very complex interaction of the environmental or nurture factors and the nature or genetic parameters. Research has established the association between genes and phenotype characteristics. However, it is not yet clear how the chemical and metabolic pathways function exactly to create a cause effect relationship. The exact role which genetic polymorphism plays in exercise, in individual sport and team sport still needs to be researched. This suggests that attempts by direct to consumer genetics testing by some companies to identify talent and establish what sports novice athletes may be suited for through genetic profiling is rather early and not valid. In the same vain, linking sport and exercise stress to individuals' genetic disposition also requires further research.

REFERENCES

Ablij, H.C. and Meinders, A.E. (2002), C-reactive protein: history and revival, *European Journal of Internal Medicine,* Vol.13, No.7 pp. 412–422.

Ahmetov, I.I. and Fedotovskaya, O.N. (2015). Current progress in sports genomics, *Advances in Clinical Chemistry*, Vol. 70, pp. 247–314.

Al – Hinai, A.T., Hassan, M.O., Simsek, M., Al – Barwani, H. and Bayoumi, R. (2002). Genotype and allele frequencies of angiotensin converting enzyme (ACE) insertion/deletion polymorphism among Omanis, *Journal for Scientific Research. Medical Sciences,* Vol. 4, No. (1-2), pp. 25 – 27.

Amir, O. Amir, R. and Yamin, R. (2007). The ACE deletion allele associated with Israeli elite endurance athletes, *Experimental Physiology,* Vol. 92, No. 5, pp. 881-886.

Avloniti, A.A., Douda, H.T., Tokmakidis, S.P., Kortsaris, A.H., Papadopoulou, E.G. and Spanoudakis, E.G. (2007). Acute effect of soccer training on white blood cell count in elite female players, *International Journal of Sports Physiology and Performance*, Vol. 2, No. 3, pp. 239-249.

Bailey, J.A., Gastin, P. B. Mackey, L. and Dwyer, D. B. (2017). The player load associated with typical activities in elite netball, *International Journal of Sports Physiology & Performance*, Vol. 12, No. 9, pp. 1218-1223.

Barros, M. P., Ganini, D., Lorenço-Lima, L., Soares, C. O., Pereira, B., Bechara, E. H. and Souza-Junior, T. P. (2012). Effects of acute creatine supplementation on iron homeostasis and uric acid-based antioxidant capacity of plasma after Wingate test, *Journal of the International Society of Sports Nutrition*, Vol. 9, No. 1, pp. 25.

Batzer, M.A. and Deininger, P.L. (2002). Alu repeats and human genomic diversity, *Nature Reviews Genetics*, Vol. 3, No. 5, pp. 370-379.

Bekris, E., Gioldasis, A., Gissis, I., Anagnostakos, K. and Eleftherios, M. (2015). From reparation to competitive period in soccer: Hematological changes, *Sports Science Review*, Vol. 24, No.1-2, pp. 103-114.

Bell, W., Colley, J.P., Evans, W.D., Darlington, S.E. and Cooper, S.M. (2012). *ACTN3* genotypes of Rugby Union players: Distribution, power output and body composition, *Annals of Human Biology*, Vol. 39, No.1, pp. 19–27.

Bhagi, S., Srivastava, S., Sarkar, S. and Singh, S. B. (2013). Distribution of performance-related gene polymorphisms (ACTN3 R577X and ACE ID) in different ethnic groups of the Indian Army, *Journal of Basic and Clinical Physiology and Pharmacology*, Vol. 24, No. 4, pp.225 -234.

Bradley, P.S. and Noakes, T.D. (2013). Match running performance fluctuations in elite soccer: indicative of fatigue, pacing or situational influences? *Journal of Sports Sciences,* Vol. 31, No.15, pp.1627-1638.

Bray, M. S., Hagberg, J. M., Perruse, L., Rankinen, M., Roth, S. M., Wolfarth, B. and Bourchard, C. (2009). The Human Gene Map for Performance and Health – Related Fitness Phenotypes, the 2006-2007 Update, Medicine *and Science in Sports and Exercise*, No.41, No.1, pp. 34 – 72.

Brewer, M. Davis., J. and Kear, J. (1994). A comparison of rugby league forwards and backs, *Journal of Sports Science*, Vol. 12, pp 158.

Brites, F. D., Evelson, P.A., Christiansen, N. G., Nicol, M. F., Basílico M.J., Wikinsiki, R. W. and Llesuy, S. F. (1999). Soccer players under regular training show oxidative stress but an improved plasma antioxidant status, *Clinical Science*, Vol. 96, No. 4, pp. 381-385.

Calo, C. M. and Vona, G. (2008). Gene polymorphisms and elite athletic performance, *Journal of Anthropological Sciences*, Vol.86, pp. 113-131.

Carninci, P. and Hayashizaki, Y. (2007). Noncoding RNA transcription beyond annotated genes, *Current Opinion in Genetic Developments*, Vol. 17, No.2, pp. 139-144.

Campbell, P.T., Campbell, K.L., Wener, M.H., Wood, B.L., Potter, J. D., McTiernan, A. and Ulrich, C. M. (2009). A yearlong exercise intervention decreases CRP among obese postmenopausal women, *Medicine and Science in Sports and Exercise,* Vol. 41, No. 8, pp. 1533-1539.

Chandler, P.T., Pinder, S., Curran, J.D. and Gabbett, T.J. (2014). Physical demands of training and competition in collegiate netball players, *Journal of Strength and Conditioning Research*, Vol.10, pp. 2732-2737.

Cięszczyk, P., Leonska-Duniec, A., Maciejewska-Skrendo, A., Sawczuk, M., Leznicka, K., Contro, V. and Lulinska -Kuklik, E. (2016). ACE gene variation in football players, *Human Movement,* Vol.17, No.4, pp. 237–241.

Coelho, D.B., Pimenta, E., Rosse, I.C., Veneroso, C., Becker, L.K., Carvalho, M.R. and Silami-Garcia, E. (2016). The alpha-actinin-3 r577x polymorphism and physical performance in soccer players, *Journal of Sports Medicine and Physical Fitness*, Vol.56, No. 3,

pp. 241-248.

Collins, C. (2018). Resistance training, recovery and genetics: AMPD1 the gene for recovery, *Journal of Athletic Enhancement*, Vol. 6, No. 2, pp.1-2.

Daray, L.A., Laura, A., Henagan, T.M., Zanovec, M., Earnest, C.P., Conrad, P., Johnson, L.G., Lisa, G., Winchester, J., Tuuri, G. and Stewart, L.K. (2011). Endurance and resistance training lowers C-reactive protein in young, healthy females, *Applied Physiology, Nutrition & Metabolism*, Vol. 36, No. 5, pp. 660–670.

Davids, K. and Baker, J. (2007). Gene's environment and sport performance, *Sports Medicine*, Vol. 37, No. 11, pp. 961-980.

Delmonico, M. J., Kostek, M. C., Doldo, N. A, *et al*. (2007). Alpha–actinin-3 (ACTN3) R577X polymorphism influences knee extensor peak power response to strength training in older men and women, *Journal of Gerontology Applied Biological Science and Medical Science*, Vol. 62, pp. 206-212.

De Moor, M. H., Spector, T. D., Cherkas, L. F., Falchi, M., Hottenga, J. J., Boomsma, D. I. and De Geus, E. J. (2007). Genome-wide linkage scan for athlete status in 700 British female DZ twin pairs, *Twin Research and Human Genetics*, Vol. 10, No. 6, pp. 812–820.

Dennis, C. (2005). Rugby team converts to give genes test a try, *Nature*, Vol. 434 No. 7031, pp. 260.

de Villiers, J.E. and Venter, R.E. (2014). Barefoot training improved ankle stability and agility in netball players, *International Journal of Sports Science & Coaching*, Vol. 9, No.3, pp. 485-495.

Devrnja, A. and Matković, B.R. (2018). The effects of a soccer match on muscle damage indicators, *Kinesiology*, Vol. 50, No. 1, pp. 112-123.

Dewannieux, M., Esnault, C. and Heidmann, T. (2003). LINE-mediated retrotransposition of marked, Alu sequences, *Nature Genetics*, Vol. 35, No.1, pp. 41-48.

Donges, C.E., Duffield, R. and Drinkwater, E.J. (2010). Effects of resistance or aerobic exercise training on interleukin-6, C-reactive protein, and body composition,*Medicine and Science in Sports and Exercise,* Vol. 42, No. 2, pp. 304-313.

Eynon, N., Banting, L.K., Ruiz, J.R., Cieszczyk. P., Dyatlov, D.A., Maciejewska-Karlowska, A., Sawczuk, M., Pushkarev, V. P., Kulikov, L. M., Pushkarev, E. D., Femia, P., Stepto, N. K., Bishop, D. J. and Lucia, A. (2014). ACTN3 R577X polymorphism and team-sport performance: a study involving three European cohorts, *Journal of Science and Medicine in Sports*, Vol. 17, No. 1, pp.102-106.

Fallon, K.E., Fallon, S.K. and Boston, T. (2001). The acute phase response and exercise: court and field sports, *British Journal of Sports Medicine, Vol.* 35, No. 3, pp. 170–173.

Fedotovskaya, O.N., Danilova, A.A. and Akhmetov, I.I. (2013). Effect of AMPD1 gene polymorphism on muscle activity in humans, *Bulletin of Experimental Biology and Medicine*, Vol.154, No. 4, pp. 489-491.

Feng, A. -F, Liu, Z. -H, Zhou, S. -L, Zhao, S. -Y, Zhu, Y. and Wang, H.-X. (2017). Effects of AMPD1 gene C34T polymorphism on cardiac index, blood pressure and prognosis in patients with cardiovascular diseases: a meta-analysis, *BMC Cardiovascular Disorders*, Vol.17, No, 174, pp.1-9.

Ferreira, M. A. and Spamer, E. J. (2010). Biomechanical, anthropometrical and physical profile of elite university netball players and relationship to musculoskeletal injuries, *South African Journal for Research in Sport, Physical Education and Recreation*, Vol. 32, No.1, pp.57-67.

Foksinski, M., Gackoski, D., Rozalski, R., Siomek, A., Guz, J., Szpila, A., Dziaman, T. and Olinski, R. (2007). Effects of basal level antioxidants on oxidative DNA damage in

humans, *European Journal of Nutrition*, Vol. 46, No. 3, pp. 174-180.

Fox, A., Spittle, M., Otago, L. and Saunders, N. (2013). Activity profiles of the Australian female netball team players during international competition: Implications for training practice, *Journal of Sports Science,* Vol.31, No.1, pp. 588– 1595.

Gabay, C. and Kushner, I. (1999). Acute-phase proteins and other systemic reverse endothelial vasomotor dysfunction in patients with responses to inflammation, *New English Journal of Medicine,* Vol. 340, No. 6, pp. 448–454.

Gatterer, H., Schenk, K., Wille, M., Murnig, P. and Burtscher, M. (2013). Effects of massage under hypoxic conditions on exercise-induced muscle damage and physical strain indices in professional soccer players, *Biology of Sport,* Vol.30, No. 2, pp. 81-83.

Giannini, D.T., Kuschnir, M.C.C., de Oliveira, C.L. and Szklo, M, M. (2017). Waist-to- Height ratio as a predictor of c-reactive protein levels, *Journal of the American College of Nutrition*, Vol. 36, No. 8, pp. 624-630.

Gineviciene, V., Jakaitiene, A., Pranculis, A., Milasius, K., Tubelis, L. and Utkus, A. (2014). AMPD1 is associated with physical performance of sprint and power in elite Lithuanian athletes, BMC *Genetics*, Vol. 15, No.58, pp.1-9.

Gabbett. T. J., (2005). Science of rugby league football: A review, *Journal of Sports Science*, Vol. 23, No. 9, pp. 961-976.

Gabbett, T., Kelly, J. and Pezet, T. (2007). Relationship between physical fitness and playing ability in Rugby league players, *Journal of Strength and Conditioning Research*, Vol. 21, No. 4, pp. 1126-1133.

Gibson, W. T. (2009). Key Concepts in Human Genetics: Understanding the Complex phenotype, in Collins, M. (Ed.), *Genetics and Sports*, Karger, Cape Town, pp.1-10.

Gleeson, M. and Walsh, N.P. (2012). The BASES Expert Statement on Exercise, Immunity and Infection, *Journal of Sports Sciences*, Vol.30, No.3, pp. 321-324.

Goh, K. P., Chew, K., Koh. A., Guan, M., Wong, Y. S. and Sum, C. F. (2009). The relationship between ACE gene ID polymorphism and aerobic capacity in Asian rugby players, *Singapore Medical Journal*, Vol. 50, No.10, pp. 997-103.

Gomez-Gallego, F., Santiago, C., Gonza´lez-Freire, M., Yvert, T., Muniesa, C.A., Serratosa, L., Altmae, S., Ruiz, J.R. and Lucia, A. (2009). The C allele of the AGT Met235Thr polymorphism is associated with power sports performance, *Applied Physiology, Nutrition and Metabolism,* Vol. 34, No. 6, pp. 1108-1111.

González, D., Marquina, R. and Rondón, N. (2008). Effects of aerobic exercise on uric acid, total antioxidant activity, oxidative stress, and nitric oxide in human saliva, *Research in Sports Medicine*, Vol.16, No. 2, pp. 128-137.

Guth, L. M. and Roth, S.M. (2013). Genetic influence on athletic performance, *Current opinion in Pediatrics*, Vol. 25, No. 6, pp. 653 -658.

Hadžović-Džuvo, A., Pjanić, S., Mekić, A. and Kapur, E. (2011). Effect of acute exercise on uric acid serum levels in the experimental model, *Homo Sportticus*, Vol. 2, pp. 12-15.

Hayashino, Y., Jackson, J.l., Hirata, T., Fukumori, N., Nakamura, F., Fukuhara, S., Tsujii, S. and Ishii, H. (2014). Effects of exercise on C-reactive protein, inflammatory cytokine and adipokine in patients with type 2 diabetes: a meta- analysis of randomized controlled trials, *Clinical and Experimental Metabolism,* Vol. 63, No. 3, pp. 431-440.

Head, S.I., Chan, S., Houweling, P.J., Quinlan, K.G.R., Murphy. R., Wagner, S., … North, K.N. (2015). Altered Ca2$^+$ Kinetics Associated with αActinin-3 Deficiency May Explain Positive Selection for ACTN3 Null Allele in Human

Evolution, *PLoS Genetics,* Vol. 11, No.1.

Heikkila, K., Ebrahim, S. and Lawlor, D.A. (2007). A systematic review of the association between circulating concentrations of C-reactive protein and cancer, *Journal of Epidemiology Community Health,* Vol.61, No. 9, pp. 824-33.

Hervert, S.R., Deakin, G.B. and Sinclair, K. (2014). A comparison of seasonal fitness of female adolescent netball and soccer players, *Journal of Australian Strength and Conditioning*, Vol. 22, pp. 116-119.

Hoff, J. (2005). Training and testing physical capacities for elite soccer players, *Journal of Sports Sciences*, Vol.23, No. 6. pp. 573-582.

Houweling, P.J., Papadimitriou, I.D., Seto, J.T., Perez, L.M., Del Coso, J., North, K.N., Lucia, A. and Eynon, N. (2018). Is evolutionary loss our gain? The role of ACTN3 Arg-577Ter (R577X) genotype in athletic performance, ageing, and disease, *Human Mutation*, Vol.39, pp. 1774 – 1787.

Hu, F.B., Meigs, J.B. Li, T.Y., Rifai, N. & Manson, J. F. (2004). Inflammatory markers and risks of developing type 2 diabetes in women, *Diabetes,* Vol.53, pp. 693-700.

International Human Genome Consortium. (2001). Initial sequencing and analysis of the human genome, *Nature*, Vol. 409, No. 6822, pp. 860-921.

IOM (Institute of Medicine). (2011). Perspectives on biomarker surrogate endpoint evaluation: Discussion forum summary. The Academies Press, Washington, DC.

Jabs, W.J., Busse, M., Krüger, S., Jocham, D., Steinhoff, J. and Doehn, C. (2005). Expression of C-reactive protein by renal cell carcinomas and unaffected surrounding renal tissue, *Kidney International,* Vol. 68, No.5, pp. 2103-2110.

Kakanis, M.W., Peake, J., Brenu, E.W., Simmonds, M., Hooper, S.L., Gray, B. and Marshall-Gradisnik, S.M. (2010). The open window of susceptibility to infection after acute exercise in healthy young male elite athletes, *Immunology Review*, Vol.16, pp. 119-1137.

Kitsios, K., Papadopoulou, M., Kosta, K., Kadoglou. N., Papagianni, M. and Tsiroukidou, K. (2013). High-sensitivity C-reactive protein levels and metabolic disorders in obese and overweight children and adolescents, *Journal of Clinical Research in Pediatric Endocrinology*, Vol. 5, No.1, pp. 44-49.

Krustrup, P., Mohr, M., Steensberg, A., Bencke, J., Kjær, M. and Bangsbo, J. (2006). Muscle and blood metabolites during a soccer game: Implications for sprint performance, *Medicine and Science in Sports and Exercise*, Vol. 38, No.6, pp. 1165-1174.

Langeveld, E., Coetzee, F.F. and Holtzhausen, L.J. (2012). Epidemiology of injuries in elite south African netball players, *South African Journal for Research in Sport, Physical Education and Recreation*, Vol.34, No. 2, pp. 83-93.

Lin, M., Tseng, C., Huang, C., Chong, C. and Tseng, C. (2001). Real - time PCR for rapid genotyping of angiotensin converting enzyme insertion/deletion polymorphism, *Clinical Biochemistry*, Vol. 34, pp. 661- 666.

Lombardi, G., Ricci, C. and Banfi, G. (2011). Effects of winter swimming on hematological parameters, *Biochemia Medica*, Vol.21 No.1, pp. 71- 78.

Lucia, A. B., Gomez-Gallego, F., Chicarro, J. L. (2005). Is there an association between ACE and CKMM polymorphisms and cycling performance status during 3-week races? *International Journal of Sports Medicine*, Vol. 26, No. 6, pp. 442-447.

Lucía, A., Morán, M., Zihong, H., and Ruiz, J.R. (2010), Elite Athletes: Are the genes the champions? *International Journal of Sports Physiology and Performance*, Vol. 5, No. 1, pp. 98-102.

MacArthur, D. G. and North K. N. (2005). Genes and human elite athletic performance,

Human Genetics, Vol. 116 No. 5, pp. 331-339.

MacArthur, D. G. and North, K. N. (2007). ACTN3: A genetic influence on muscle function and athletic performance, *Exercise and Sport Sciences Reviews,* Vol. 35, No.1, pp. 30–34.

Magalhães, J., Rebelo, A., Oliveira, E., Silva, J.R., Marques, F. and Ascensão, A. (2010). Impact of Loughborough Intermittent Shuttle Test versus soccer match on physiological, biochemical and neuromuscular parameters, *European Journal of Applied Physiology*, Vol. 108, No.1, pp. 39-48.

Martens, R. (2004), Successful Coaching (3rd edition). Champaign Illinois, USA, Human Kinetics.

Martins, R.A., Neves, A.P., Coelho-Silva, M.J., Veríssimo, M, T. and Teixeira, A. M. (2010). The effect of aerobic versus strength-based training on high-sensitivity C-reactive protein in older adults, *European Journal of Applied Physiology,* Vol. 110, No 1, pp. 161-169.

Massidda, M., Scorcu, M. and Calã, C.M. (2014). New genetic model for predicting phenotype traits in sports, *International Journal of Sports Physiology and Performance*, Vol. 9, No. 3, pp. 554-60.

Mattusch, B., Dufaux, O., Heine, I., Mertens, H. and Rost, T. (2000). Reduction of the plasma concentration of C-reactive protein following nine months of endurance training, *International Journal of Sports Medicine*, Vol. 21, No.1, pp. 21-24.

McCabe, K. and Collins, C. (2018). Can genetics predict injury? The association of the genes GDF5, AMPD1, COL5A1 and IGF2 on Soccer player injury occurrence, *Sports*, Vol. 6, No. 1, pp. 1-10.

Mclean, S., Hulme, A., Mooney, M., Read, G.J.M., Bedford, A. and Salmon, P.M. (2019). A systems approach to performance analysis in women's netball: Using work domain analysis to model elite netball performance, *Frontiers in Psychology*, Vol.10, pp. 201.

Mendham, A.E., Donges, C.E., Liberts, E.A. and Duffield, R. (2011), Effects of mode and intensity on the acute exercise-induced IL-6 and CRP response in sedentary, overweight population, *European Journal of Applied Physiology,* Vol. 111, No.6, pp.1035-1045.

Meckel, Y., Nemet, D., Alves, A.J., Eliakim, A. and Eynon, N. (2012). The AMPD1 C34T mutation is not associated with the status of Israeli athletes, *European Journal of Sports Science,* Vol. 12, No.3, pp. 244- 248.

Michigan, A., Johnson, T.V. and Master, V.A. (2011). Review of the Relationship between C-reactive protein and Exercise, *Molecular Diagnosis and Therapy,* Vol. 15, No.5, pp. 265-275.

Mills, R., Yang, N., Weinberger, R., Van der Woude, D. L., Beggs, A. H., Eastlea, S. and North, K. (2001). Differential expression of the actin-binding proteins, α-actinin-2 and -3, in different species: implications for the evolution of functional redundancy, *Human Molecular Genetics*, Vol. 10, No. 13, pp. 335-1346.

Mitchell, J.H., Haskel, W., Snell, P., Van Camp, S.P. (2005). Task Force 8: Classification of Sports, *Journal of the American College of Cardiology*, Vol. 45, No. 8, pp. 1364-1367.

Molly, E. and Chetty, T. (2015). The rocky road to legacy: Lessons from the 2010 FIFA World Cup South Africa stadium programme, *Project Management Journal*, Vol.46, No. 3, pp. 88-107.

Mora, S. Lee, I.M., Buring, J.E. and Ridker, P.M. (2006). Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women, *Journal of the American Medical Association*, Vol. 2951, pp. 412–419.

Moraes, A.A., Trape, A.A., Ferezin, L.P., Goncalves, C.P., Monteiro, C.P. and Bueno Junior, C.R. (2018). Association of ACE ID and ACTN3 C > T genetic polymorphism with response to a multicomponent training pro-

gram in physical performance in women from 50 to 70 years, *Science and Sports*, Vol. 33, No.5, pp. 282-290.

Moran, C.N., Yang, N., Bailey, M.E.S., Tsiokanos, A., Jamurtas, A., MacArthur, D. G., Wilson, R.H. (2007), Association analysis of the ACTN3 R557X polymorphism and complex quantitative body composition and performance phenotypes in adolescent Greeks, *European Journal of Human Genetics,* Vol. 15, pp. 88-93.

Morgado, J.P., Matias, C.N., Monteiro, C.P., Alves, F., Reis, J.F., Santos, D.A., Silva, M., Martins, F., Seixas, M. T., Rocha-Pereira, P., Sardinha, L. B. and Laires, M. (2016). Comparison of immunohematological profile between endurance and power-oriented elite athletes, *Applied Physiology, Nutrition, and Metabolism*, Vol. 42, No.3, pp. 257-262.

Nazarovi, I.B., Woods, D.R. and Montegomery, H.E. (2001). The angiotensin converting enzyme I/D polymorphism in Russian athletes, *European Journal of Human Genetics*, Vol. 9, No. 10, pp. 797-801.

Nazmi, S., Kadir, Y., Betul, C., Serdar, B. and Bekir, C. (2014). Effect of royal jelly ingestion for four weeks on hematological blood markers on swimmers, *Science, Movement and Health*, Vol. 14, No. 2, pp. 196-202.

Noakes, T.D. and Durandt, J.J. (2000). Physiological requirement of cricket, *Journal of Sports Science*, Vol. 18 No. 12, pp. 919-929.

Nunes, T. and Coetsee, B. (2007). The contribution of isokinetic strength parameters to the performance of cricket batsmen, *Isokinetic and Exercise Science*, Vol. 15, No. 3, pp. 233-244.

O'Connor, D., (1996). Physiological characteristics of professional rugby league players, *Strength and Conditioning Coach*, Vol. 4, pp. 21-26.

Plaisance, E.P., Taylor, J. K., Alhassan, S., Abebe. A., Mestek, M.L. and Grandjean, P.W. (2007). Cardiovascular fitness and vascular inflammatory markers and acute aerobic exercise, *International Journal of Sport Nutrition and Exercise Metabolism*, Vol. 17, No.2, pp. 152-162.

Pimenta, E. M., Coelho, D. B., Veneroso, C. E., Barros Coelho, E. J., Cruz, I. R., Morandi, R. F., De Azambuja Pussieldi, G., Carvalho, M. R. S., Garcia, E. S., De Paz Fernández, J. A. (2013). Effect of ACTN3 gene on strength and endurance in soccer players, *Journal of Strength and Conditioning Research*, Vol. 27, No. 12, pp. 3286-3292.

Pimenta, E.M., Coelho, D.B., Cruz, I.R., Morandi, R.F., Veneroso, C.E., De Azambuja Pussieldi, G., Carvalho, M.R., Silami-Garcia, E. and De Paz Fernández, J.A. (2012). The ACTN3 genotype in soccer players in response to acute eccentric training, *European Journal of Applied Physiology*, Vol. 112, No. 4, pp.1495-503.

Pitsiladis, Y.P., Tanaka, M., Eynon, N., Bouchard, C., North, K.N., Williams, A.G. Collins, M., Moran, C.N., Britton, S.L., Fuku, N., Ashley, E.A., Klissouras, V., Lucia, **A.**, Ahmetov, I.I., de Geus, E. and Alsayrafi M. (2016). Athlome Project Consortium: A concerted effort to discover and other "omic" markers of athletic performance, *Physiological Genomics*, Vol. 48, No. 3, pp. 183-190.

Powers, S. K., Ji, L. L. and Leeuwenburgh, C. (1999). Exercise training induced alterations in skeletal muscle antioxidant capacity: a brief review, *Medicine and Science in Sports and Exercise*, Vol. 31, No. 7, pp. 987-997.

Puthucheary, Z., Skipworth, J.R.A., Rawal, J., Loosemore, M., Someren, K.V. and Montgomery, H.E. (2011). Genetic influences in sport and physical performance, *Sports Medicine*, Vol. 41, No. 10, pp. 845–859.

Ricci, J.M, Flores, V. Kuroyama, I., Asher, A. and Tarleton, H.P. (2018). Pilot study of dose -response effects of exercise on change in C-reactive protein, cortisol, and health -related

quality of life among cancer survivors, *Bioresearch open Access*, Vol. 7, No. 1, pp. 52-62.

Saghebjoo, M., Nezamdoost, Z., Ahmadabadi, F., Saffari, I. and Hamidi, A. (2018). The effect of twelve weeks of aerobic training on serum levels high sensitive C-reactive protein, tumor necrosis factor-alpha profile and anthropometric characteristics in middle-aged women patients with type 2 diabetes, *Diabetes and Metabolic Syndrome*, Vol. 12, No. 2, pp. 163-168.

Salem, A., H. and Batzer, M., A. (2009). High frequency of the D allele of the angiotensin converting- enzyme gene in Arabic populations, *Bio Medical Central Research Notes*, Vol. 2, pp. 99.

Santiago. C., Gonzalez-Freire, M., Serratosa, L., Morate, F.J., Meyer, T., Gomez-Gallego, F., Lucia, A. (2008), ACTN3 genotype in professional soccer players, *British Journal of Sports Medicine*, Vol. 42, No.1, pp. 71-73.

Santi Maria, T., Arruda, M., Portella, D., Vargas Vitoria, R., Gómez Campos, R.G., Martinez, C. Cossio-Bolanos M. (2013). Hematological Parameters of Elite Soccer Players during the Competitive Period, *Journal of Exercise Physiology*, Vol. 16, No. 5, pp. 68-76.

Sarmento, H., Marcelino, R., Anguera, M.T., Campanico, J., Matos, N. and Leitao, J.C. (2014).Match analysis in football: a systematic review, *Journal of Sports Sciences*, Vol. 32, No. 20, pp. 1831-1843.

Scanavini., Bernardi, F. and Castoldi, E. (2002), Increased frequency of the homozygous 11 ACE genotype in Italian Olympic endurance athletes, *European Journal of Human Genetics*, Vol.10, No.10, pp. 576-7.

Sipahi, T., Budak, M., Sen, S., Ay, A. and Sener, S. (2006). Association between ACE gene Insertion (I)/ deletion (D) polymorphism and primary hypertension in Turkish patients of Trakya region, *Biotechnology and biotechnology Enquiry*, Vol. 20, No. 2, pp. 104-108.

Slizik, M., Pospieszna, B., Gronek, J. and Sworek, R. (2017). Are SNIP's still desirable in sport genomics? *Trend in Sport Sciences*, Vol. 1, No. 24, pp. 13-18.

Soh, K.G., Soh, K.L., Mohd.Sofian, O.F., Ong, S.L. and Noorzaliza, O. (2007). Body fat and somatotype among Malaysian school netball players by playing performance, *Asian Journal of Physical Education and Recreation*, Vol. 15, No.1, pp. 56-60.

Souglis, A., Bogdanis, G.C., Giannopoulou, I., Papadopoulos, C.H. and Apostolidis, N. (2015).Comparison of inflammatory responses and muscle damage indices following a soccer, basketball, volleyball and handball game at an elite competitive level, *Research in Sports Medicine*, Vol. 23, No.1, pp. 59-72.

Sporiš, G., Vlahović, T., Trajković, N., Milanović, Z. and Madić, D. (2016). Haematological and iron status following a soccer match, *Physical Education and Sport*, Vol. 14, No. 2, pp. 289-295.

Squire, J. M. (1997). Architecture and function in the muscle sarcomere, *Current Opinion in Structural Biology*, Vol. 7, No. 2, pp. 247-257.

Stuelcken, M., Pyne, D. and Sinclair, P. (2007). Anthropometric characteristics of elite cricket fast bowlers, *Journal of Sports Science,* Vol. 25, No. 14, pp. 1587-1597.

Suhr, F., Porten, S., Hertrich, T., Brixius, K., Schmidt, A., Platen, P. and Bloch, W. (2009).Intensive exercise induces changes of endothelial nitric oxide synthase pattern in human erythrocytes, *Nitric Oxide*, Vol. 20, No. 2, pp. 95-103.

Svensson, M. B., Ekblom, B. B., Cotgreave, I. A., Norman, B. B., Sjöberg, B. B., Ekblom, Ö., Sjödin, B. and Sjödin, A. A. (2002). Adaptive stress response of glutathione and uric acid metabolism in man following controlled exercise and diet, *Acta Physiologica Scandinavica*, Vol.176, No.1, pp. 43-56.

Tanriverdi, H., Evrengul, H., Tanriverdi, S., Turgut, S., Akdag, B., Kaftan, H. A. and Semiz, E. (2005). Improved endothelium dependent vasodilatation in endurance athletes and its relationship with ACE I/D polymorphism, *Cardiology*, Vol. 69, No. 9, pp. 1105-1110.

Tsalouhidou, S., Petridou, A. and Mougios, V. (2007). Exercise and antioxidant capacity of uric acid, *Inquires in Sport and physical Education,* Vol. 5, No. 3, pp. 451-458.

Van Hoorenbeeck, K., Franckx, H., Debode, P., Aerts, P., Wouters, K., Ramet, J., Van Gaal, L. F., Desager, K.N., De Backer, W.A. and Verhulst, S.L. (2012).Weight loss and sleep-disordered breathing in childhood obesity: Effects on inflammation and uric acid, *Obesity,* Vol. 20, No.1, pp. 172-177.

Varley, M.C., Gregson, W., McMillan, K., Bonnano, D., Stafford, K., Modonutti, M. and Di Salvo, V. (2016). Physical and technical performance of elite youth soccer players during international tournaments: influence of playing position and team success and opponent quality, *Science and Medicine in Football*, Vol. 1, No. 1, pp. 8-29.

Vincent, B., De Bock, K., Ramaekers, M., Van den Eede, E., Van Leemputte, M., Hespel, P. and Thomis, M.A.(2007). ACTN3 (R577X) genotype is associated with fiber type distribution, *Physiological Genomics*, Vol. 32, No. 1, pp. 58-63.

Yamaner, F. (2010). Oxidative predictors and lipoproteins in male soccer players, *Turkish Journal of Medical Sciences*, Vol. 40, No. 3, pp. 427-434.

Yang, N., MacArthur, D.G., Wolde, B., Onywera, V.O., Boit, M.K., Lau, S.Y., Wilson, R.H., Scott, R.A., Pitsiladis, Y.P. and North, K. (2007). ACTN3 R577X polymorphism in East and West African athletes, *Medicine and Science in Sports and Exercise*. Vol. 39, No. 11, pp.1985- 1988.

World Rugby (2017), Year in review. Retrieved from

http://publications.worldrugby.org/yearinreview2017/en/48-1 (Accessed 10 March 2019).

Wang, P., Fedoruk, M. N. and Rupert, J. L. (2008). Keeping pace with ACE are ACE inhibitors and angiotensin II type I receptor antagonists potential doping agents? *Sports Medicine*, Vol. 38, No. 12, pp. 1065-1079.

Zhang, B., Tanaka, H., Shono., N., Miura, S., Kiyonga, A., Shindo, M. and Saku, K. (2003). The I allele of the angiotensin-converting enzyme gene is associated with an increase percentage of slow-twitch type I fibers in human skeletal muscle, *Clinical Genetics*, Vol. 63, No 2, pp. 139-144.

Corresponding author:

Sam Chenjerai Mugandani
Center for Biokinetics, Recreation and Sport Science,
School of Health Sciences, University of Venda,
Private Bag X5050, Thohoyandou, South Africa
E-mail: sam.mugandani@univen .ac.za