

Influence of Genetics on Sports Injuries

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Abstract

Summary

The identification of risk factors and the assessment of athlete's predisposition to suffer an injury and the way in which it will occur is hard to predict due to the multifactorial origin of the lesions. In recent years, the importance of the genetic component of each individual as a possible cause of injury predisposition is being evaluated.

The objective of this work was to write a review of the genetic studies carried out to date on connective tissue injuries and propose future research lines that would allow the development of more personalized training programs and specify preventive therapies in order to reduce the injury risk.

The multifactorial origin of injuries complicates the identification of risk factors (extrinsic and intrinsic factors). Together, these factors and their interaction predisposes an athlete to injuries. In recent years, the genetic component of each individual as a possible cause of injury predisposition has become of importance.

The aim of this article was to propose a review of published genetic studies related to connective tissue repair or regeneration and to pave the way for future Sports Medicine Research. This information could be very useful in order to individualize the preventive strategies to avoid injuries and to optimize the therapeutic and rehabilitation process after injuries.

Applied biology is already contributing new knowledge by providing new biomarkers that will give information and increase understanding regarding the susceptibility of individuals to suffer certain types of injury. Genetic analysis can offer us reliable and objective predictive parameter that combined with the current methods of analysis will help improve the performance and management of athletes.

Keywords: Genetic polymorphism; Connective tissue; Sport injuries, Lesions

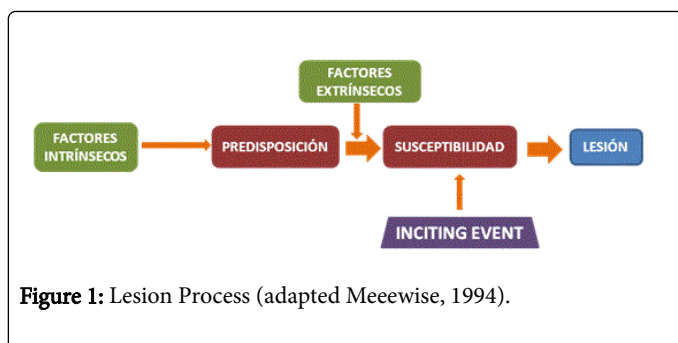
Introduction

Physical and athletic performance depends on both biological properties and mechanical properties of the tissues. Exposure to high levels of competition entails a considerable risk of injury due to the high level of physical and psychological demands and loading involved. The effects of injuries extend beyond just the injured athlete or player. The coaches, the team, the sponsors and the clubs also become affected [1].

Scientifically labelling real risk factors and designing protocols with fatigability indexes is one of the objectives of the sports medicine [2,3]. Different methods are being used to diagnose fatigue. Blood tests are complemented by the use of global positioning systems (GPS) systems [3]. GPS systems used in training and matches provide information regarding the physical output (and often also the physiological loading) associated with each individual player in every session. Information

regarding the number of sprints, acceleration and decelerations movement patterns, number of high intensity actions and cardiorespiratory information can all provide valuable information. Extrinsic factors (EF) such as field of play, ball characteristics, sports equipment, poor planning as well as intrinsic factors (IF) such as previous injuries, muscle imbalances, lack of flexibility, interact resulting in injury. The IF gives us a predisposition to injury but that alone does not guarantee an injury. The IF interacts with a set of EF and this increases susceptibility to damage, but this occurs only with the contact of a trigger element [4]. Ultimately, the sum of IF and EF is indicative of a probability of risk of injury (Figure 1).

A high number of non-contact injuries (injuries that do not occur as a result of blows, external trauma or impacts) compromises the ability of a player to perform or may result in a player being unable to compete. The direct consequences negatively impact not only the individual but also the collective unit and the possibility of achieving set individual and group goals and objectives.



The prevalence of non-contact injuries can be decreased by implementing and monitoring different injury prevention strategies and working on the 'prevention rather than cure philosophy'. Prevention programs must be developed to minimize the effect of the different risk factors, reduce the incidence of injuries and/or at the same time try to reduce their severity.

Historically, the focus has been on injury history, biochemical and metabolic indicators, tomographic, anthropometric and nutritional information. These, however, have proven insufficient to help reduce the number of non-contact injuries, especially muscle injuries.

Nowadays, progress is being made in the study and application of genetics in the world of sport, and the genetic analysis of athletes can offer us reliable and objective predictive parameter that combined with the current methods of analysis will help improve the performance and management of athletes.

Genetic Variation and Detection Methods

Nucleotide variations in the genetic code are responsible for the modulation of responses to external stimuli. These variations, called polymorphisms occur in 1% of the population and may be given various types tandem repeats (microsatellites), deletions, insertions, duplications and alterations of one base (SNPs - single nucleotide polymorphisms).

SNPs are the most common variations, accounting for 90% of the changes produced in the genome and occurring every 100-300 base pairs. They are variations of a single base in the DNA sequence that are found in low frequency within population but whose presence is important enough to be considered, since they may or may not influence the phenotype of the individuals giving rise to a biomarker of clinical utility. Because of the influence on the phenotype of athletes, it is crucial and highly informative to make use of genetics as a complement to the parameters studied so far. These SNPs can be found in both promoter (regions composed of specific DNA sequences located just where the transcription starting point is located) and exon regions (regions encoding a particular protein) of the genes. SNPs can also be found in the intergenic (non-coding DNA) or intronic (nucleotide removed during RNA splicing). Any of these cases may result in an alteration of the final genetic product. This occurs either due to an alteration in the final confirmation of the protein or due to an increase or a decrease in messenger RNA (mRNA) levels which will result in more or less elevated protein levels [5].

It is necessary to obtain the individual's DNA to detect the presence of SNPs. Sampling for subsequent extraction and purification of the DNA can be performed in different ways, including from biological fluids such as blood or saliva. Once the sample is collected, the DNA is

extracted using already established protocols. There are several methods for detecting the presence of SNPs, but the most common is the use of restriction enzymes or using the technique of allelic discrimination assays. Restriction enzymes recognize a nucleotide sequence within a DNA molecule and cut it at that particular point (restriction target). This method has one major limitation in that it generates a lot of false positives leading to problems when interpreting the results. Using allelic discrimination assays is more precise and with a relatively small amount of DNA it is possible to differentiate between three types of populations: wild-type, heterozygous and homozygous for the SNP. Generally, the analysis is performed using fluorescently labelled TaqMan probes. The technique is based on real-time polymerase chain reaction (PCR), which detects the emitted fluorescence at each amplification cycle. This fluorescence makes it possible to discriminate between the three types of populations we have discussed previously (Figure 2) [5].

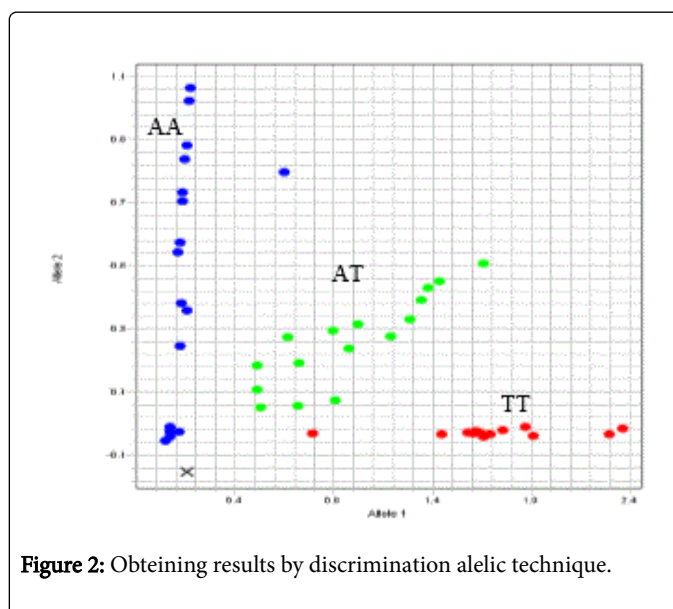


Figure 2: Obtaining results by discrimination allelic technique.

Recent studies have shown the importance of the individual genetic component, considered as an IF, in the non-contact injuries produced in the soft tissues [6-9]. All these studies indicate that there is a strong (more than 50%) genetic influence on the nature of injuries occurring. Other studies show that the presences of these variations in DNA are related to injuries produced in the connective tissue although most of these studies have been performed in non-sports population [10-13].

Genetics and Injury Occurrence

Most sports-related injuries occur in soft tissues, affecting muscles, tendons and ligaments, and about 90% of them are non-contact injuries.

Currently, soft tissue injuries are considered connective tissue injuries [14]. A Tissue is damaged and subsequently repaired, and for this process to be correct, a set of proteins and growth factors synthesized by genes related to the repair and regeneration of connective tissue are involved. The presence of SNPs in these genes could alter these processes and explain why there are injuries of greater or lesser severity and why the recovery times for the same injury may vary between individuals.

This research group attempted to establish the relationship between SNPs present in genes related to repair and regeneration of connective tissue and the severity of injuries produced in a group of professional footballers, as well as the possible relationship with recovery times.

The first study [15] was performed with DNA obtained from a population of 73 elite players. The number and classification of non-contact muscle, tendon and ligament injuries occurring over 3 consecutive seasons was recorded. A mild injury is classified as one in which less than 25% of the connective tissue is affected. An injury is severe when more than 50% of the connective tissue of that structure is affected. Any other injury is considered as moderate injuries. In this study the EFs were controlled as much as possible. The players were subjected to the same methodology and load of training, they competed in the same competitions, had the same schedules and physical work times, trained and competed in identical conditions and temperature since they live and train in the same city, were exposed to the same diet and hydration patterns, and had identical administration schedules of vitamin supplements. The study was focused on the influence of genetic factors which are classified as IFs. A relationship between the polymorphisms studied in the IGF-II (insulin-like growth factor II) and CCL2 (chemokine ligand 2) genes was observed with the severity of the muscle injury. IGF-II plays an important role in the growth of soft tissue tissues and participates in the activation of satellite cells, increasing their expression in response to post-injury degeneration and regeneration processes [16,17]. CCL2 is a cytokine produced by macrophages and by satellite cells that participates in muscle repair and adaptation processes [18]. Players with GC genotype for the IGF-II gene had muscle injuries. Likewise, CC/GC genotype players for the CCL2 gene had fewer severe injuries than those with GG genotype. In addition, study we have shown that 3 SNPs in Hepatocyte Growth Factor gene (HGF) are directly related with injury rate, severity and recovery time for muscle injuries [19]. We also found a relationship between the polymorphism studied in ELN (elastin) and the severity and recovery time of ligamentous injuries. The absence of elastin or poorly constituted protein distorts the presentation and stability of other components of the extracellular matrix and the interactions, making the ELN very important for elastogenesis and functioning of living in elastic fibers [20]. In this case, players with AA genotype are more prone to severe injuries and take much longer to recover from them than those with AG/GG genotypes. When injured and during repair and regeneration the contractile function is lost and cellular differentiation takes place towards the immature elastin phenotype capable of proliferating and depositing in the extracellular matrix. A recent study have shown that SNPs in Elastin gene are correlated with a greater severity of ligament injuries [21], indicating that could be a novel biomarker for the detection a priori of this kind of injuries.

A follow-up study we analyzed whether the injury patterns in different race groups could be affected by the presence of SNPs [22]. Several studies showed that some diseases progress differently depending on the ethnic group to which the patient belongs [23,24]. In the world of professional sports, and especially in professional football, the constant search of the best players for each specific position of game has resulted in teams scouting players of different nationalities and ethnic groups. The globalization of the game made it relevant to analyze injury patterns based on race. The study looked at how race could fuel developments of specialized injury recovery and prevention protocols as well as more individualized training protocols.

The study found that the frequency of occurrence of SNPs varied in the three populations studied. This variability should be considered in order to analyze and study the etiopathogenesis of soft tissue non-contact injuries, in order to be able to apply personalized exercises as it is currently done with some diseases [25].

An ongoing project is currently establishing SNPs' relationships with the injury rate in order to identify those players who are more prone to injury. In this way it could be possible to get a complete profile of every player including main characteristics relating to injury such as injury rate, type and severity of injury and the time required for recovery.

Applicability and Utilization of Genetic Testing

The studies previously mentioned have led to the development of a Genetic Injury Test. Genetic analysis provides predictive, reliable, objective and invariable information applied to professional sports and contributes to injury prevention and performance enhancement of athletes.

In order to conduct the test a sample of blood or saliva is taken and the genetic material is extracted and purified. Once the DNA is obtained The SNPs are analyzed using the allelic discrimination assay (as previously mentioned).

There are two case studies that highlight the process. There was a case of a 54 year old, male amateur sportsman and tennis fan. He would practice 3-4 days a week for the last 20 years. During the last 2 years he had repeatedly undergone processes of muscular fibrillation, in thighs of both legs (hamstrings and quadriceps). He has always been injured just by running. Lower extremity dysmetria and other joint pathologies were ruled out. In each process, the same procedure had been followed: ultrasound diagnosis, physical rest, physiotherapy treatment and sports rehabilitation with muscle stretching before and after physical activity. Even so, he had been repeatedly injured. Eventually he underwent the Genetic Injury Test. The study of the biomarkers confirmed a genetic predisposition to suffer muscle-tendon injuries as well as the presence of alterations in the structural bases of collagen, a condition that results in weakness in muscle tissues as well as fatigue and joint pain. From the results obtained this athlete has followed training of short duration and high intensity, a supplementation with hydrolyzed collagen, chondroitin and glucosamine and a re-planning of applied loads, thus improving their physical state.

Another case involved a 28 year old male who was a professional motor racer. The results of his genetic test indicated that he was predisposed to severe muscle injuries with high recovery times and a tendency to suffer fatigue and joint pain due to the inadequate assimilation of the loads applied to it. Knowing these results, performing personalized exercises increased the ability of his body to better assimilate the loads both during training and competition and with the administration of adequate supplementation, this driver became world champion in 2015.

Conclusions

To date, epidemiological studies have proven to be the most useful tool to acquire knowledge and obtain information on the prevalence of soft tissue injuries. They help to detect risk factors that may be involved in these injuries in order to develop and implement preventive strategies. Recently, genetics has illuminated and guided the search for

new biomarkers that would enable the identification of more objective risk factors.

Genetic studies are part of the modern medicine and should be applied in the fields of sport medicine, specially focused on injury risk biomarkers and treatment responses [26]. In order to advance, it is necessary to have homogenous populations to be able to carry out an exhaustive monitoring to correlate and validate the genetic studies with the reality of the sport practice.

Currently the biomarkers routinely used to attempt to correlate the rates of injury are focused on the information provided by blood tests. Thus, hemoglobin, ferritin, creatinine, urea, transaminase, CK and ionograms are obtained from time to time. An athlete is considered to be in a state of "fragility" or fatigue, and consequently more susceptible to injury, when hemoglobin levels are below 15 g/dl, ferritin levels are less than 50 ng/ml, levels. Elevated levels of urea and creatinine compared to the reference levels indicated, transaminase levels above 60 IU/L and CK levels Higher than 600 IU/L. In addition, values of hyper-hypokalemia and hypomagnesaemia also relate to situations of physical fragility of the athlete. Despite all this information, this method of determining the physical condition of the athlete is not 100% reproducible as it depends on the medical criteria of the professionals of the different teams. It is essential to look for a system which can, in the most objective way possible, relate the cause of an injury and the recovery time

Applied biology and genetics are already contributing new knowledge by providing new biomarkers that will help provide information and increased understanding regarding the susceptibility of individuals to suffer certain types of injuries, be considered good or bad responders related to a specific treatment or planing a recovery procediment when modulating loads. The connective tissue quality (determined by the genetic profile) is key point to tolerate and withstand training and competition loads

Limitations and Lines for the Future

The studies cited above are based on results obtained after studying and monitoring 73 professional soccer players, and despite being a relatively small population, it was a homogenous population and the study was conducted in a highly controlled environment which adds an important value to the existing information. It would be difficult to increase the population in this type of study given the characteristics of the participants in them and the control of the study.

This study of new biomarkers will result in more effective injury prevention protocols and management of training/competition loads by adapting possible weaknesses in relation to musculoskeletal injuries. On the other hand, these biomarkers could, in the near future, provide useful information regarding return to play following injury.

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