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Review Article

Genes Can Express Injury Propensity and Recovery Pace in Sports

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Abstract

One of the main threats of competitive sports is painful injuries. Athletes' joints are vulnerable and they are exposed to frequent injuries. Genetic variations contributing to the onset of musculoskeletal injuries, particularly in tendon and ligament tissues, have been identified and these impact the athletic performance [1]. For instance, in tendons and ligaments, genes encode production and remodelling of collagen fibers (COL1A1, COL12A1 and COL5A1, MMP3), modulate their elastic and biomechanical properties (TNC, ELN), as well as influence their growth differentiation factors (GDF5, IGF2). Thus their unfavourable expressions can pose a risk for tendinopathy. Exercise/sports activity triggers a local, systemic inflammatory cascade with a release of both pro- and anti-inflammatory cytokines (such as TNFα, IL-6, CRP). The balance between them decides the recovery pace for a sport-induced injury. Genes determine the degree of body's response to enhance repair and recovery processes after exercising. And injury recovery capacity is decisive in determining the amount of rest period required between exercises. Thus genetic variations fundamentally influence the susceptibility for sport-related injuries and the innate recovery potential. And this insight is much needed for implementing preventive and coping strategies [2]. Among other options used by trainers, physicians and athletes, nutritional support tailor-made to suit the genetic makeup may help enhance recovery.

Keywords: Gene; Genetic Variations; Mutation; Allele; Injury-Susceptible Allele; Single Nucleotide Polymorphism/SNP; Flexibility; Tendinopathy; Gene-Specific Nutrients

Flexibility is directly proportional to ease of movement in a sport

Flexibility is the ability to move muscles and joints effectively through a complete range of motion. The following figure (Figure 1) illustrates the role of various physiological components in flexibility.

Why is flexibility important in sports?

- Performing stretching exercises before any fitness activity allows the body to become more flexible and less prone to injury.
- Stretching after exercise is also equally important as it allows the muscles to get back to their normal form and helps in reducing muscle soreness and pain.
- The degree of flexibility and risk for tendinopathy can be determined through genes and this insight will guide an athlete in deciding the type and duration of pre and post stretching exercises to make his fitness regimen comfortable [3,4].

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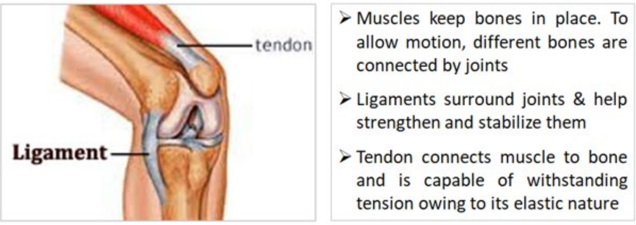

- Muscles keep bones in place. To allow motion, different bones are connected by joints
- Ligaments surround joints & help strengthen and stabilize them
- Tendon connects muscle to bone and is capable of withstanding tension owing to its elastic nature

Figure 1: Role of various physiological components in flexibility.

What is tendinopathy and how does it relate with genes?

Tendinopathy refers to painful conditions occurring in and around tendons in response to overuse. It results from an imbalance between the protective/regenerative changes and the pathologic responses that result from tendon overuse. The net result is tendon degeneration, weakness, tearing, and pain. To combat tendinopathy, there occurs expression of protective factors such as insulin-like growth factor 1 (IGF-1) and nitric oxide synthetase (NOS). The efficiency of these protective factors is based on the expression of their encoding genes [5-8].

Genetic influence of tendon and ligament injuries in athletes

The following four factors explain how certain genes can influence the propensity for sport-related tendon and ligament injuries through their varied expressions.

- Production of various collagen fibers in tendons and ligaments
- Extracellular matrix glycoproteins modulate the elastic and biomechanical properties of tendons and ligaments
- Regulation of remodelling the collagen fibers in tendons and ligaments
- Degeneration and regeneration of musculoskeletal soft tissues like tendons as regulated by growth factors

Each factor is explained in detail in the following sections.

Genes like COL1A1, COL12A1 and COL5A1 encode production of various collagen fibers in tendons and ligaments – which maintains their structural integrity and normal mechanical function.

Gene (SNP: rsid)	Mode of action	Protective allele	Injury susceptible allele	Gene-specific nutrients to cope with injury susceptible allele
COL5A1 (rs12722) [9]	encodes type-V collagen formation which is a minor fibrillar collagen found in ligaments and tendons, contributing to flexibility	C allele renders greater flexibility and a decreased risk for tendinopathy	T allele is associated with less flexibility and an increased risk for tendinopathy	Collagen-strengthening anthocyanins, glutathione, vitamin C, Methionine, Cysteine and Taurine [10-15] Food sources include beetroot, pink radish, purple cabbage, broccoli, strawberries and blackberries to name a few. Branched chain amino acids (BCAA) including leucine, isoleucine and valine stimulate collagen synthesis in the muscle [16,17] Vitamin B6 and Vitamin E enhance tendon health [18-20] Pre and post exercise stretching, and random exercising of different muscle groups can also prove beneficial [21]
COL1A1 (rs1800012) [9]	Encodes Collagen type I fibrils which majorly constitute bone matrix forming strong parallel bundles of fibers in tendons and ligaments	T allele reduces risk of cruciate ligament ruptures, shoulder dislocation ruptures and Achilles tendon ruptures	G allele results in production of a weaker type I collagen which increases susceptibility for tendinopathy	
COL12A1 (rs240736) [9]	Encodes production of Type XII collagen, a structural component of the ligament fibril	T allele reduces the susceptibility for ligament tear/injury	A allele increases risk of developing anterior cruciate ligament injury by 2.4 fold, especially in females	

Table 1

Extracellular matrix glycoproteins like tenascin and elastin modulate the elastic and biomechanical properties of tendons and ligaments.

Gene (SNP: rsid)	Mode of action	Protective allele	Injury susceptible allele	Gene-specific nutrients to cope with injury susceptible allele
ELN (rs2289360) [9,22]	This gene shows association with the degree of ligament injuries. Encodes Elastin/ ELN, a self-assembling extracellular matrix protein, is the major source of tissue elasticity	G allele relates to more efficient elastin function and hence requires shorter recovery time	AA genotypes suffer more severe injuries and require longer recovery times	Vitamin A and vitamin C replenish elastin levels [24] Genistein, a type of soybean isoflavone, is a phytoestrogen which supports tissue elasticity [25] Gelatin rich foods including meat, bone broths, yoghurt and agar-agar maintain elastin levels [26] Copper increases the activity of the enzyme lysyl oxidase, which helps in the cross-linking of collagen and elastin. Organ meat, shellfish, cashews, almonds, sunflower seeds and lentils are among its sources [27]
TNC (rs2104772) [23]	Encodes tenascin-C which modulates the elastic and biomechanical properties of tendons and ligaments. Its expressed predominately in regions responsible for transmitting high levels of mechanical force	T allele reduces the susceptibility for such injuries	A allele increases risk of Achilles tendon injuries and rotator cuff injury	

Table 2

MMP3 gene encodes matrix metalloproteinase which regulates remodelling of collagen in tendons and ligamnets.

Gene (SNP: rsid)	Mode of action	Protective allele	Injury susceptible allele	Gene-specific nutrients to cope with injury susceptible allele
MMP3 (rs679620) [9]	Encodes matrix metalloproteinase which regulates remodelling of collagen in tendons and ligaments. Aids in recovery by degrading denatured structural collagen	A allele (AA or AG genotype) combined with the COL5A1 rs12722 CC genotype had the lowest risk for Achilles tendinopathy	G allele increases the risk of Achilles Tendinopathy due to reduced MMP3 activity	MMPs are zinc dependent, hence zinc supplementation improves their catalytic activity [28-30] Polyphenols, carotenoids, and flavonoids also enhance MMPs activity

Table 3

Degeneration and regeneration of musculoskeletal soft tissues like tendons is regulated by genes like GDF5 and IGF2.

Recovery pace for sports-related injuries [34-38]

Depending on duration and intensity, exercise will cause damage to the muscle resulting in disarrangement in fiber structures, loss of fiber integrity, and leakage of muscle protein. Trying to restore homeostasis, several repair processes start, involving inflammation, resolution, muscle repair, and finally regeneration. Exercise triggers a local and systemic inflammation with a release of both pro- and anti-inflammatory cytokines. The balance between them decides the outcome of repair and regeneration. The following figure (Figure 2) explains the need for a balance in pro- and anti- inflammation.

Gene (SNP: rsid)	Mode of action	Protective allele	Injury susceptible allele	Gene-specific nutrients to cope with injury susceptible allele
GDF5 (rs143383) [9]	‘Growth/Differentiation Factor 5’ is involved in the maintenance, development and repair of bones, cartilage and other musculoskeletal soft tissues including tendons	C allele carriers have a decreased risk for tendinopathy	T allele carriers have an increased propensity for tendinopathy due to reduced expression of this gene in tendons	Beta-palmitate present in milk improves GDF5 levels, aiding in recovery of sport-related muscle injury [31]
IGF2 (rs3213221) [9,32]	encodes insulin-like growth factor 2 whose role is significant in soft tissue growth. Gene expression increases in response to degeneration and regeneration following an injury. SNPs relate with severity of muscle injuries.	A allele relates with lesser chance for muscle injuries following sports, and is seen in endurance-type sport players	G allele carriers are more prone to ankle and knee injuries in sorcerers, and consequently play less number of matches	Essential amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine) help maintain favourable levels of insulin-like growth factors [33]

Table 4

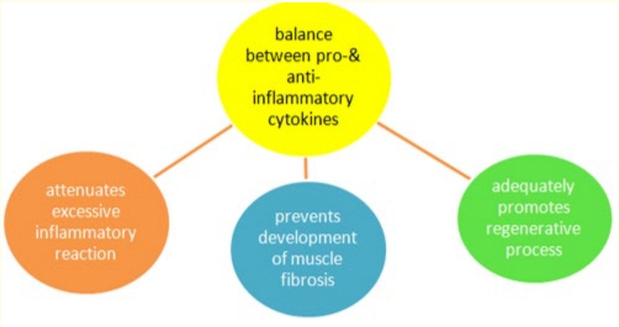

Figure 2: The need for a balance in pro- and anti- inflammation.

Genes determine the recovery pace of sports-related inflammatory injuries

Our genes determine the degree of body’s response to enhance repair and recovery processes after exercising. Injury recovery capacity helps in determining the amount of rest period required between exercises. Genes regulated after exercise are involved in inflammation, cellular communication, signal transduction, cellular protection, growth, and repair. Let’s understand how this happens through the following examples.

Regulation of body’s inflammatory response through cytokines after a sport is dependent on genes like TNFα, IL6, CRP. They encode cytokines which induce inflammatory muscle injury when triggered in excess. Variations in these genes decide the extent of muscle repair after an inflammatory injury that can be induced by exercise.

Extent of muscle repair after an exercise-related inflammatory injury is determined by genes like CCL2 which encodes chemokine, CC motif, ligand 2 (CCL2) taking part in muscle repair and adaptation.

Recovery pace as determined by free radical quenching

During exercise, oxidative stress is linked to muscle metabolism and muscle damage, because exercise increases free radical production. Hence genes regulating antioxidant enzymes are also of concern in determining the recovery pace of sports injury.

Genetics plays an integral role in athletic performance and is increasingly becoming recognised as an important risk factor for injury propensity and recovery pace. For athletes, time lost from

Gene (SNP: rsid)	Mode of action	Quick recovery allele	Slow recovery allele	Gene-specific nutrients to cope with slow recovery allele
TNFα (rs1800629) [39]	Encodes production of cytokine, Tumor Necrosis Factor Alpha	G allele is associated with a reduced inflammatory response to exercise. GG genotype can exercise longer and recover quicker from sports injuries	A allele carriers take longer time to restore the balance between pro- and anti- inflammatory markers after exercise. require longer rest periods to recover before the next training session	Probiotics and omega-3 fatty acids reduce proinflammatory cytokines [41-44]
IL-6 (rs1800795) [37,39]	Encodes production of interleukin which majorly contributes to inflammatory response that is upregulated during ligament and tendon injuries	G allele relates to reduced susceptibility for exercise-induced inflammatory muscle injury	C allele corresponds with greater risk for exercise-induced inflammatory muscle injury	
CRP (rs1205) [37,39,40]	Encodes C reactive protein, an exercise recovery marker. There is a short-term, transient increase in serum CRP after strenuous exercise which is a part of exercise-induced inflammation	In A allele carriers, serum CRP levels triggered by exercise blunt soon and hence pose reduced risk for exercise-induced inflammatory muscle injury	G allele carriers have significantly higher levels of CRP triggered after exercise. Hence linked with greater risk for exercise-induced inflammatory muscle injury	

Table 5

Gene (SNP: rsid)	Mode of action	Quick recovery allele	Slow recovery allele	Gene-specific nutrients to cope with slow recovery allele
CCL2 (rs2857656) [45,46]	Encodes chemokine, CC motif, ligand 2 (CCL2). CCL2 is a small chemokine produced by macrophages and plays key roles in inflammation and immunoregulation. CCL2 expression increases dramatically following muscle damage and takes part in muscle repair and adaptation	CC and CG genotypes are associated with less severe muscle injuries	G allele is related to markers of muscle injury, such as creatine kinase and myoglobin levels. GG genotype is associated with muscle pain	Omega-3 fatty acids and Epigallocatechin-3-Gallate (EGCG) present in green tea balance chemokine levels aiding in muscle recovery after a sports activity [47-49]

Table 6

Gene (SNP: rsid)	Mode of action	Quick recovery allele	Slow recovery allele	Gene-specific nutrients to cope with slow recovery allele
SOD2 (rs4880) [50,51]	encodes manganese superoxide dismutase (MnSOD), which supports the dismutation of mitochondrial superoxide radicals into hydrogen peroxide and oxygen.	C allele relates with efficient SOD2 activity and hence suitable for faster recovery	T allele reduces SOD2 efficiency against oxidative stress, and is associated with increased creatinine kinase level (a muscle damage marker) post-exercise.	Manganese can improve the catalytic activity of this metalloenzyme. Additionally, Vitamin A, C and E quicken recovery with their regenerative properties [52-56]

GSTP1 (rs1695) [57-59] Glutathione S-transferase P1	Encodes Glutathione S-transferase (GST), a phase II detoxifying enzyme crucial for cellular protection against oxidative stress	G allele renders better elimination of exercise-induced ROS/Reactive Oxygen species, hence less prone to muscle damage	A allele relates with an impaired ability to remove excess reactive oxygen species and hence more prone to muscle damage	Selenium and tripeptide glutathione increase this enzyme's catalytic activity [60] Curcumin (150-1500 mg/day) before and during exercise, and up until 72 h' post-exercise, improves performance by reducing exercise-induced muscle damage and modulating inflammation [61]

Table 7

training and competition due to injury has a profoundly negative impact on performance. And hence, minimising time loss from injury, through a personalised approach has been correlated with athletic success for both teams and individuals.

Injuries are an inescapable aspect of exercising and participation in sport. The particular results of an exercise-induced injury may vary widely depending on the nature and severity of the injury. Injuries typically result in cessation, or at least a reduction, in participation in sport and decreased physical activity. Recent evidence suggests that half of the total number of injuries can be considered severe, leading to an average of >3 weeks without training or competing [62]. Sport injuries cause health-related costs in excess of $1 billion dollars worldwide. It is estimated that 3–5 million sports injuries occur in a year, according to data from the United Nations. Thus, interventions like gene-specific nutritional recommendations which might increase the rate of healing and decrease the time to return to play are important [63].

Future research perspectives and practical implications

Any athletic activity is synonymous with physical movements, still the group of muscles/anatomical region that are most used differs from sport to sport. For instance, in soccer players, ankle and knee injuries are the commonest, while tennis players are more susceptible to rotator cuff injury (rotator cuff refers to the group of muscles and tendons that stabilize the shoulder joint). This fact translates into an application-oriented field called 'kinesiogenomics' which is emerging to minimize and manage sport-related injury. Kinesiogenomics understands the physiology of human movement through the indulgence of genetics to achieve 'sport-related' injury prevention. Citing a practical scenario, the TNC gene encodes tenascin-C which modulates the elastic and biomechanical properties of tendons and ligaments. Its expression is altered in the presence of a single nucleotide polymorphism, rs2104772, which makes its 'A' allele carriers more susceptible for rotator cuff injury. A young tennis aspirant can benefit from this genetic insight as their training sessions can emphasize on strengthening the rotator cuff by performing specific exercises like shoulder external rotation with a resistance band, and positioning the wrist/forearm slightly upward to maintain an exact 90 degrees angle of bend at their elbow throughout the movement, amongst other expert techniques. Additionally, such pre-participation screening can guide their sports nutritionist to focus on nutrients like genestein (from soya products) to improve their tissue elasticity. Use of genomic information has potential benefits in elite athletes as the training team is better equipped with their innate tendencies on aspects like adaptation to a sport, injury propensity and recovery pace. This is a much-needed practical tool for personalizing training and nutritional requirements [64,65]. Physical education curriculum and sports training programs should include sports genetics as an integral part as students can understand the importance of innate tendencies and align their sports preferences accordingly. Right from an early age, the essentiality of gene-specific nutrition and personalized training can be emphasized.

Physical performance trait is polygenic, hence large cohorts should aim at studying the additive effect of pathway genes. For instance, while analysing the genetic influence on collagen fiber production in tendons and ligaments, though COL5A1 is the most-researched, variations in COL1A1 and COL12A1 should not be ignored. Future research should also be geared up to quantify the beneficial effects of overcoming genetic set-backs through sports-nutrigenetics and personalized training. Such beneficial effects should be researched in innumerable categories of sports and replicated in various populations [66].

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