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Anterior cruciate ligament injury, could it also be a matter of genetics?

Nicolas Bechaud[1] and Florian Forelli[1,2,3*]

[1]Physical Therapist, Orthosport Rehab Center, 16 rue de Paris, Domont, France

[2]Researcher Physical Therapist, Ramsay Santé, Clinic of Domont, 85 route de Domont, Domont, France

[3]Physical Therapist, CDFAS, High Performance Sports Medical Center, 64 Rue des Bouquinvilles, Eaubonne, France

Corresponding E-mail: fforelli@capio.fr

ABSTRACT

Background*: Genomics is a science, which for decades has enabled us to study the variability of the genetic material of every living being. Using new Genome Sequencing Technologies (GWAS), research has demonstrated the impact of our genetic material on the risk of injury, especially in athletes.*

Methods: *Variants of several genes and combinations of genes have been associated with an altered risk of anterior cruciate ligament injury. An anterior cruciate ligament rupture would be twice as likely in a person with a family history of anterior cruciate ligament rupture.*

In this review of the literature, we attempted to establish a list of genes that would be involved in the risk of anterior cruciate ligament injury and to understand how.

Results: *COL1A1, COL3A1, COL5A1, COL12A1, GDF5, MMP, ELN, FBN-2, VEGFA, KDR, NGFB, HIF1A, ACAN, BGN, DCN, FMOD, LUM, Il-1B, Il-6 or even TNF, are as many genes or combinations of genes which code for proteins playing a role in the size and composition of muscle fibers, flexibility, structures and functions of tendons and ligaments but also in signaling pathways such as angiogenesis, inflammation and fibrillogenesis.*

Conclusion: *This study also serves to focus on genetic screening for the follow-up, support and prevention of athlete injuries*.

Keywords: Genomics, Genes, ACL, Genetic screening, Prevention, Injuries

Abbreviations: ACAN: Aggrecan Proteoglycan; ACE: Angiotensin I Converting Enzyme; ACL: Anterior Cruciate Ligament; ACTN-3: Alpha-Actinin III; AMPD-1: Adenosine Monophosphate Deaminase I; AluI: Restriction Enzyme; BGN: Biglycan; BstUI: Restriction Enzyme; COL1A1: Collagen Type I Alpha 1 Chain; COL3A1: Collagen Type III Alpha 1 Chain; COL5A1: Collagen Type V Alpha 1 Chain; COL12A1: Collagen Type XII Alpha 1 Chain; COLGALT1: Procollagen Galactosyltransferase 1; DCN: Decorin, DpnII: Restriction Endonuclease; ELN: Elastin; FBN2: Fibrillin 2; FMOD: Fibromodulin; GDF5: Growth Differentiation Factor 5; GWAS: Genome-Wide Association Study; HIF1A: Hypoxia Inducible Factor 1 Subunit Alpha; Il-1B: Interleukin 1-B; Il-6: Interleukin 6; KDR: Kinase Insert Domain Receptor; LUM: Lumican; MMP : Matrix Metalloproteinase; NGFB: Nerve Growth Factor Beta; NID1: Nidogen 1 (Formerly Entactin); RLFP: Restriction Fragment Length Polymorphism; SNP: Single Nucléotid Polymorphism; TGF-bêta: Transforming Growth Factors β; TNF: Tumor Necrosis Factor; VEGFA: Vascular Endothelial Growth Factor A

INTRODUCTION

The ACL injury remains one of the most publicized injuries in the sports world. Despite the economic blow it causes for professional and non-professional structures, this injury causes significant physiological and psychological changes which directly impact the return to play. Today, optimizing rehabilitation seems to involve changing the physical and clinical capacities of patients while taking into account the preventive aspects of iterative or contralateral injury. The preventive aspect especially emphasizes the study of the mechanisms of ACL injury which has made it possible to highlight biomechanical perturbation associated with neurocognitive pertubation. If the preventive protocols in terms of muscle strengthening and proprioceptive have shown effectiveness in the prevention of ACL lesions and injuries in general, the fact remains that certain avenues seem to be put forward to date in this type of lesion: the study of the human genome.

DESCRIPTION OF THE IMPACT OF GENETICS ON THE RISK OF INJURY

Genomics is a science, which for decades has enabled us to study the variability of the genetic material of every living thing. Many factors, such as training, nutrition, motivation, but also genetics and epigenetics, are responsible for the performance of an athlete. This is no longer to be demonstrated, our genetic passport influences strength, power, endurance (in particular the ACE and ACTN-3 genes) but also the size and composition of muscle fibers, flexibility, neuromuscular coordination, temperament and other phenotypes [1].

In his study, McCabe et al. [2], determines that certain genes are linked to the occurrence of injuries, regardless of athletic level. The AMPD1 gene (encoding the protein adenosine monophosphate deaminase 1) has been shown to be linked to a need for increased recovery after strenuous activity. Those who take this rest have better performance [3]. Indeed, this genetic variability determines the structure and function of tendons and ligaments, which influences and modifies the risk of injury for every human being. Certain combinations of genetic variants (of proteins, such as collagen, which play structural and functional roles in tendons and ligaments) and susceptibility to ACL injury have been discovered in recent years [4].

We are in an exciting time for sports genomics. Thanks to new technologies (whole Genome Sequencing, GWAS) but also bioinformatics (to dissect and analyze more in depth) we will be able to better understand which DNA polymorphisms/mutations are involved, by what mechanisms and routes they exert effects on human physical capacity [1].

Correlation between Risk of ACL Injury and Genetics

Over the past 30 years, many studies have attempted to examine the genetic susceptibility to predispose an individual to ACL injury. ACL injury would be twice as likely in a person with a family history of ACL injury [4]. Magnusson et al. [5] go further and find that the genetic contribution to ACL injury is approximately 69%; the same risk increases from 20% to 140% if a sibling has an ACL injury. Other studies [6-8] have shown this familial predisposition. The majority of research on the genetics of ACL injury has involved GWAS.

From these studies, variants of several genes were associated with a change in the risk of ACL injury [4]. Collagen fibrillation (fibrillogenesis), the basic element of ligaments, will determine, by its arrangement and its integrity, the dynamic, elastic and biomechanical properties of the ACL. Fibrillation is also composed of proteoglycans such as aggrecan (the main proteoglycan of articular cartilage), fibromodulin (small interstitial proteoglycan), biglycan (which affects the development and regeneration of muscles, bone growth and fibril assembly. of collagen in many tissues), lumican (distributed in interstitial collagen matrices throughout the body) and decorin (which affects the assembly of collagen fibrils) [9].

Genes Involved In the Risk of ACL Injury

ACL injury is believed to be a highly polygenic trait [10]. No less than nine SNPs in eight genes involved [11] in different physiological pathways and mechanisms associated with ACL injury have been discovered. In this part, we will try to establish a list of genes that, according to the literature, are involved in the rupture of the ACL and understand how (summarized in Table 1).

Table 1 Study table of genetic associations with ACL tears.

Genes	Study	Population	Participants	Conclusions
	Khoschnau et al.	Sweden	No ethnicity reported. 233 participants with cruciate ligament injury, 126 participants shoulder dislocations, 325 female controls.	People with the TT genotype had a reduced risk of injury for cruciate ligament ruptures and shoulder dislocations compared to carriers of GG.
	Posthumus et al.	South Africa	Caucasian, 117 participants with ACL rupture, 130 for the control group.	The TT genotype is under-represented in the ACL injury group

				compared to the control group.
COL1A1 (rs1800012)				
	Ficek et al.	Poland	Caucasian, 91 professional soccer players with ACL injury - all non-contact, 143 professional soccer players (good health) as control group.	No differences in genotypes. There was an overrepresentation of G-T haplotypes (1997G + 1245T) in the control group, suggesting that carriers may have a reduced risk of injury.
	Stephien-Słodkowska et al.	Poland	No ethnicity reported, 138 male recreational skiers with ACL injury, 183 apparently healthy male skiers as controls.	Carriers of the GG genotype had a lower risk of ACL injury than carriers of the TT genotype.
	Stephien-Slodkowska et al.	Poland		The AA genotype was overrepresented in the ACL group compared to controls.
COL3A1 (rs1800255)	O'Connell et al.	South Africa (SA)/ Poland	Caucasian. 333 participants with ACL injury (242 SA and 91 Poland), 378 apparently healthy controls (235 SA and 143 Poland).	No difference in the distribution of genotypic frequencies between the SA LCA group and the SA control group. However, the AA genotype was over-represented in the Polish LCA group compared to Polish controls. No association of alleles for any of the groups.
	Kim et al.	Caucasian, Latin America, Asian (East), African, Asia (South East).	5148 participants with Achilles tendon injury, 97,831 apparently healthy controls, 598 participants with ACL injury, 98,744 apparently healthy controls.	No association after Benjamini-Hochberg correction to test multiple hypotheses.

COL1A1

The COL1A1 gene encodes a chain of proteins in type I collagen, a major structural component of ligaments. In particular, the polymorphism of the COL1A1 gene (rs1800012) has been associated with a reduced risk of sports-

related tendon or ligament injuries, especially in ACL injuries in different population cohorts [12-14]. In the vast majority of cases, the G nucleotide is present. However, for 20% of the population, T is present, resulting in the TT genotype. The TT genotype leads to qualitatively superior type 1 collagen fibers [15]. Only the study by Stepien-Slodkowska [16] presents different results; Carriers of the GG genotype had a lower risk of ACL damage than carriers of the TT genotype.

COL3A1

Type III collagen is an important factor in connective tissue repair, and some gene polymorphisms can alter tensile strength. In all the studies, an association between the polymorphism of the COL3A1 gene (rs1800255) and the risk of ACL rupture would be possible but without being, however, highly significant. This association would be even more likely, depending on ethnicity (Poland>South Africa) [11,17,18].

COL5A1

The COL5A1 gene encodes the alpha-1 protein chain of type V collagen, which is involved in the formation of connective tissue in the musculoskeletal system. People with a T allele of this gene have been shown to be at increased risk of injury. According to Stępień-Słodkowska et al. [19], the combination of the BstUI RFLP (rs12722) C-T and DpnII (rs13946) RFLP C-T polymorphisms, would reduce the risk of ACL injury (in the control group of male skiers) because the C-T genotype is underrepresented. While in his study Posthumus et al. [20] a significant difference exists in the distribution of the C-C genotype of COL5A1 BstUI RFLP which is underrepresented in women with ACL injury. In rugby players [21], the combination of the two C-C genotypes (rs12722 and rs3196378) would decrease the risk of injury.

COL12A1

Type XII collagen belongs to a family of non-fibrillar collagens that are associated with the surface of the fibril and is encoded by a single gene, COL12A1 (chromosome 6q12-q1355). Like type V collagen, it is believed to regulate the diameter of fibrils (fibrillogenesis) [22]. The A-A genotype of the COL12A1 AluI RFLP gene in exon 65 is associated with a risk of ACL rupture in women [23]. While in the Indian population, the A-G and G-G genotypes in exon 65 are associated with ACL tears [24]. In his study, Ficek et al. [25], obtained no significant results.

MMP

Several matrix metalloproteinase genes, including those which are physiological mediators of collagen cleavage and elimination, are located on chromosome 11q22. In the literature, several studies have proposed to study the polymorphism of MMP1 genes. According to Posthumus et al. [26], MMP1 genotypes are associated with the risk of ACL rupture. For Malila et al. [27], the MMP3 genotype is over-represented in ACL tears. While for Gibbon et al. [28], do not obtain any significant results concerning the genotype of MMP3 and the rupture of ACL, same for Lulińska-Kuklik et al. [29], although, their results support the hypothesis that genetic variation within MMP3 contributes to inter-individual susceptibility to non-contact ACLR. In addition, Lulinska-Kuklik et al. [30] sought to

demonstrate the influence of other variants within the MMP10 and MMP12 genes on the risk of ACL injury, but without success.

GDF5

GDF5 (Growth Differentiation Factor 5) encodes proteins of the TGF-beta (Transformative Growth Factor-Beta) family. This protein regulates the development of many types of tissues and cells, including cartilage, joints, brown fat, teeth, and the growth of axons and neuronal dendrites. The study by Chen et al., showed that the GDF5+104T/C polymorphism was associated with patients with ACL injury in central China [31]. This is probably due to reduced levels of the GDF5 protein in players carrying the TT genotype, resulting in disruption of ligament homeostasis. While for Raleigh et al. [32], the rs143383 polymorphism was not associated with the risk of ACL injury.

ELN+FBN2

Elastin (ELN) is an insoluble polymer composed of several molecules of tropoelastin which contributes to the elasticity of tendons and ligaments (stretching and return to the initial state) and plays an important role of load support in musculo-tissue -skeletal (where mechanical energy is stored). Fibrillins, FBN-1 and FBN-2 (important role in the assembly of elastic fibers), are large glycoproteins found in the extracellular matrix of tendons and ligaments and are involved in providing strength and flexibility. Alone, the polymorphism of the FBN2 (Fibrillin-2) gene has been associated with both Achilles tendon and ACL injury [33].

VEGFA+KDR+NGFB+HIF1A

Signaling Pathway for Angiogenesis The angiogenesis signaling pathway is fundamental to the remodeling of the extracellular matrix in response to the application of mechanical load. Several genes encode the protein components thereof: Vascular Endothelial Growth Factor Isoform a (VEGFA), Kinase Insertion Domain Receptor (KDR), Nerve Growth Factor (NGF) and the factor inducible by Hypoxia-1α (HIF1A). They show particular interest in the study of sensitivity to ACL lesions. The VEGFA rs699947 C-C genotype was significantly over-represented in participants with non-contact ACL rupture. The VEGFA rs1570360 G-A genotype was significantly over-represented in the control group. In addition, the G-A KDR rs2071559 genotype was significantly overrepresented in women in the control group. These results suggest that the VEGFA and KDR genes may be involved and therefore show the biological importance of the angiogenesis signaling pathway in the pathophysiology of ACL injuries [34]. Cięszczyk's study [9] also highlights the importance of research into the impact of this signaling pathway in ACL injuries.

ACAN+BGN+DCN+FMOD+LUM

Fibrillogenesis In the process of fibrillogenesis, proteoglycans (a combination of a protein and a polysaccharide chain) play an important role. They also help maintain the structural integrity of ligaments. The genes encoding these are: polymorphisms within the genes encoding the Aggrecan of Proteoglycans (ACAN), Biglycan (BGN), Decorin (DCN), Fibromodulin (FMOD) and Lumican (LUM). They have been shown to be linked to sensitivity to ACL injuries. Mannion hypothesizes that the variability of the genetic sequence within genes encoding

proteoglycans could potentially modulate the properties of ligamentous fibrils [35]. Again, Cięszczyk's study [9] highlights the importance of further research on these genetic loci.

Il-1B+Il-6+TNF

Inflammatory route It is the trio of pro-inflammatory cytokines of innate immunity. Interleukin-1 β is the main endogenous pyrogen, it induces the synthesis of prostaglandins, the influx and activation of neutrophils, the activation of T cells and the production of cytokines, the activation of B cells and the production of antibody, as well as fibroblast proliferation and collagen production. Interleukin 6 acts as a messenger between the cells involved in this process. Overproduction of IL6 and its Receptor (IL6R) causes inflammation and joint damage. TNF-α plays a pro-inflammatory role both on its own and by regulating other inflammatory mediators such as Il1-B and Il6. It intervenes at the cellular level, where it promotes the recruitment of lymphocytes and neutrophils as well as the detection of antigens, and at the tissue level where it participates in tissue remodeling and repair. To date, only one study has demonstrated a link between two associations of genetic polymorphism (COL5A1-IL1B-IL6 T-C-G and COL5A1-IL1B-IL6R T-C-A) of the inflammatory pathway and an increased risk of ACL lesions. This relationship was only observed for male participants [36]. This study shows that these polymorphisms modulate the expression of structural components and components of the extracellular matrix, associated with fibrils, contributing to an increased susceptibility to ACL injury.

Other Genes Showing Interest

According to Brazier [4], several genetic variants recently identified in a GWAS [10] (Genome-Wide Association Study), deserve to be studied, in more detail in the future, such as COLGALT1 rs8090 and NID1 rs4660148. These variants are believed to be strongly associated with ACL rupture, but nothing significant on the human genome scale. As Kaynak et al. [37], progress regarding the association between genetic variants and ACL injury suggests that in a few years we will be able to understand all of these mechanisms.

Genetic screening and iterative risk

It is no longer to be demonstrated, ACL reconstruction offers a higher incidence of new knee injuries, whatever the type, a risk factor for recurrence in the graft (11.3 times more in the 12 months) but also a risk factor for ACL injury of the contralateral knee (with or without contact) [8,38].

In 2012, September et al. [39], already mentioned the principle of personalized medicine. This is based on tailor-made clinical management of a patient based on his genetic and non-genetic medical profile. The idea is to improve the quality of care through more comprehensive diagnostics. For this, screening by genetic testing would be necessary. The effectiveness of these targeted therapies would depend on the clinician's ability to interpret the tests. Increasingly, in the literature [1,2,4], it is proposed to use genetic screening to prevent the risk of injury but also to improve the management and management of injuries. Indeed, sports clubs would have a better understanding of the sensitivity of athletes to certain pathological

conditions (injuries, cardiomyopathies, sudden death, etc.), could map the genetic fit to specific positions and roles within a team, and gain insight into athlete development in various sports or physical activities. It would also make it possible to personalize the training and nutrition of each athlete. To date, some laboratory allows this screening and this support. The cost of the test is not negligible but could decrease the cost of healthcare for every human being in the long run.

CONCLUSION

The sequencing of the human genome seems to be an interesting solution in the context of the detection of ACL injury and on a larger that of injury of the musculoskeletal system. Although its use remains little exploited, our study of the literature highlights a certain number of factors that can interact with ACL injury. Knowing the athlete in a holistic and unique approach could make it possible in the long term to be informed but above all to highlight "invisible" deficiencies that irreparably cause harm to our patients. Thus, the supervisory teams could adapt or adopt new prevention protocols based on the study of genetic sequencing. More and more reliable clinical evaluation devices are being used in the world of sport to map our athletes, so why not sequence the human genome? The question deserves to be asked.

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