Genetic Aspects in Shoulder Disorders*

Aspectos genéticos nas afecções do ombro

Carina Cohen[1] Eduardo A. Figueiredo[1] Paulo S. Belangero[1] Carlos Vicente Andreoli[1] Mariana Ferreira Leal[2] Benno Ejnisman[1]

[1] Sports Medicine and Physical Activity discipline, Sports Traumatology Center, Universidade Federal de São Paulo, São Paulo, SP, Brazil
[2] Biomedical Department of Morphology and Genetics, Universidade Federal de São Paulo, São Paulo, SP, Brazil

Address for correspondence Carina Cohen, PhD, Avenida Lineu de Paula Machado, 660, Jd Everest, São Paulo, SP, 05601-000, Brazil (e-mail: cacohen18@gmail.com).

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Abstract

The influence of genetic inheritance has been increasingly investigated in shoulder disorders, such as rotator cuff injury, instability and frozen shoulder. Although the initial findings are enlightening, it is necessary to progressively build a database of genetic markers to catalog genomic profiles that, later, may contribute for predicting the risk of the disease, as well as to the development of better diagnostic and treatment tools. The present article seeks to update what is evidence of genetic studies in the literature for these diseases, from polymorphism analyses, expression of candidate genes in tissues and broad genomic association studies (GWAS). However, it is necessary to point out that there is great difficulty in replicating and using the findings, mainly due to the lack of statistical power, the high rate of false-positive results and the large number of variables involved.

Keywords
- shoulder
- genetic polymorphism
- gene expression

Resumo

A influência da herança genética tem sido cada vez mais investigada nas afecções do ombro, como a lesão do manguito rotador, instabilidade e ombro congelado. Ainda que os achados iniciais sejam pouco esclarecedores, é necessário construir progressivamente um banco de marcadores genéticos para catalogar perfis genômicos que, mais adiante, poderão contribuir para a previsão do risco da doença, desenvolvimento de melhores ferramentas de diagnóstico e tratamento. O presente artigo busca atualizar o que há de evidências de estudos genéticos na literatura para essas doenças, desde análises de polimorfismos, expressão de genes candidatos em tecidos e estudos de associação genômica ampla (GWAS, na sigla em inglês). Porém, é necessário apontar que existe grande dificuldade na replicação e utilização dos achados, principalmente em razão da falta de poder estatístico, da alta taxa de resultados falso-positivos e da grande quantidade de variáveis envolvidas.

Palavras-chave
- ombro
- polimorfismo genético
- expressão gênica

* Work developed in the Sports Medicine and Physical Activity Discipline, Sports Traumatology Center (CETE, in the Portuguese acronym), Universidade Federal de São Paulo (UNIFESP, in the Portuguese acronym), São Paulo, SP, Brazil.

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Introduction

The influence of genetics has been increasingly investigated in shoulder disorders, such as rotator cuff injury (RCI), instability and frozen shoulder (FS). Because they are complex or multifactorial diseases, these lesions are determined by the interaction of genetic and environmental factors. A characteristic of complex diseases is that they may present family aggregation, as it is more likely that the relatives of an affected person will share with them more alleles of predisposition to the disease than unrelated people.

The genome of any 2 individuals of the human species are identical in 99.9% of its sequence.[1] Thus, the difference between individuals represents 0.1% of the genome. Among the variations, when the frequency of an allelic variant reaches $>$ 1% of the population, this variant is called "polymorphism". The most frequently studied types are single nucleotide polymorphisms (SNPs). There are several drawings of studies appropriate for genetic research of multifactorial diseases such as twin studies, adoption studies, family studies, studies of trios (purpose, mother and father) and case-control studies.[2]

For musculoskeletal system injuries, most published studies investigate the frequency of polymorphism of "candidate genes" in cases and controls based on literature publications. Case-control studies can also be conducted on a large scale, such as genome wide association studies (GWAS), which use robust sequencing techniques or *microarray* (oligonucleotide *chips)* to scan genetic variants (usually hundreds of thousands of SNPs) into a human genome. Genome wide association studies are essentially a hypothesis-free approach because they make no assumptions about the location or functional meaning of associated loci or their products.[2] It should be noted that, in addition to studies based on DNA analysis, gene and protein expression studies can provide clues to involved genes and the knowledge of the biological function of these genes can help in understanding the molecular pathophysiology of the disease.

Most studies that evaluated whether genetic variants are associated with the risk of shoulder lesions investigated polymorphisms in genes encoding proteins present in the extracellular matrix (ECM) or which are directly or indirectly involved in homeostasis and repair process of the tissues involved (ligaments, tendons, and capsule) whose basic structure is the collagen fibril. Variants in collagen genes can alter the primary structure of the collagen, generating chains less stable than normal, in order to affect the capsular structure. The fibrils of the articular tissues are composed predominantly by type I collagen, which is primarily responsible for physiological resistance to tension. During the process of repairing tendons and ligaments, it is postulated that collagen III forms a primary architecture that is subsequently infiltrated and replaced with collagen I.[3] Type V collagen is a fibrinogenesis regulator and intersperses in type I collagen fibers, so that its alteration can generate structural damage to the capsule as suggested in individuals with Ehlers Danlos syndrome whose *COL5* expression was decreased in between 25 and 30% of the patients with mutation of this gene.[4]

Additionally, other collagens, collagen synthesis modulator genes (*TGFB, TGFB1*), metalloproteinases, proteoglycans that may be associated with fibrils and glycoproteins – for example, fibronectin (FN) and tenascin C (*TNC*),which act in the modulation of TGFB and in the tendon repair process by promoting migration and adherence of fibroblasts to fibrils.[5,6] Cytokines, such as TGFB1 and its receptors, can play a key role in inflammatory and fibrotic processes, regulating various ECM proteins, including collagens, FN1 and TNC.[7] It is undoubtedly one of the cytokines most closely involved in the fibrosis process, and is present in large quantities in places of chronic inflammation.[8]

Matrix metalloproteinases (MMPs) are zinc-dependent proteases responsible for tissue remodeling and the degradation of ECM during normal physiological processes such as cell proliferation, remodeling of tissues, reproduction, differentiation, angiogenesis and apoptosis, but also participate in diseases such as arthritis, tumor invasion, cancer and inflammation, and may harm the organization and structural support of the tissues.[9] These enzymes are classified based on their substrate preference, including collagenases (e.g., MMP1 and MMP13), strobes (e.g. MMP3) and gelatinases (e.g., MMP2 and MMP9). Matrix metalloproteinases are inhibited by a class of proteins called TIMP.

Rotator Cuff Injury

Despite the theories of intrinsic and extrinsic causes for the origin of rotator cuff injuries (RCIs), there is preliminary evidence of genetic contribution leading to tendinous degeneration and consequent rupture of the tendons.[10]

Studies in the literature show that siblings of individuals with RCI are more likely to develop complete injury and risk of being symptomatic.[11–14] Recently, in a study with 33 pairs of elderly twins (17 monozygotics and 16 dizigothics), Gumina et al.[15] calculated the heritability rate of 18%, and the contribution of 44% to the shared environment and 38% to the single environment. Gene expression studies demonstrate different gene behaviors in relation to rotator cuff injury. Riley et al.[16] evaluated 10 patients and 24 controls and found decreased expression of the *MMP2, MMP9, MMP13* genes.

Lo et al.,[17,18] in a study with tissue of 10 patients and 6 cadavers, found increased expression of *MMP13* and inhibition of *MMP3* expression, *TIMP2*, *TIMP3*, *TIMP4*. In 2005, the same author found an increase in the expression of *MMP13*, *COL1A1*, *COL3A1* and agrecan, in addition to inhibition of the expression of decorine.

Shindle et al.[19] found increased expression of *MMP9*, *MMP13*, *COX2* and *COL1A1* as well as decreased expression of iNOS, *VEGF*, *COL3A1* and biglican. Shirachi et al.[20] analyzed the expression of *COL1A1* and *COL3A1* at the edge of the lesion of the supraspinal tendon in 12 patients, with five fresh cadavers as control. The authors correlated the expression of these genes with the integrity of the repair after the period of 1 year postoperatively. In addition, the expression of *COL1A1* was associated with the time of onset of symptoms, suggesting that conservative treatment should not be

prolonged if patients do not present improvement after a certain period.

Robertson et al.[21] evaluated the gene expression of pro-inflammatory cytokines, tissue remodeling genes and angiogenesis factors in 35 patients with complete RCI. There was a correlation of increased expression of MMP1 and MMP9 and failure of repair healing. Gotoh et al.[22] performed a study with 24 patients and found an increase in *MMP3* and *TIMP1* expression in patients who had re-rupture after 1 year of RCI repair. The expression of collagen genes was not related.

The first genetic study conducted by national authors observed a correlation between RCI and polymorphisms in the genes *DEFB1, ESRRB, FGF3, FGF10* and *FGFR1*. The authors also concluded that female and white gender are the main predictors of this type of injury. [23] Confirming these findings, mutations of the *ESRRB* gene were correlated with the lesion in a study with 175 patients with RCI compared to a control group of 3,293 individuals from a genetic database access open for consultation (*Illumina iControls database*). [24] It is noteworthy that this series of cases did not distinguish patients with traumatic and degenerative injuries.

Tashjian et al.[25] used information from a population genetic database containing a sample of 311 cases compared with 2,641 healthy individuals and found a relationship between mutations in *sap30BP* genes and *SASH1* in RCI. Both genes have a direct relationship with the apoptosis mechanism.

In another publication performed in a Brazilian population, 64 patients with RCI were evaluated and the association with genetic polymorphisms of *MMP-1* and *MMP-3* metalloproteinases were evaluated.[26]

Sejersen et al,[27] in a systematic review, identified 2,199 protein analysis studies in tendinopathies and verified a tendency to increase COL1, COL3, MMP1, MMP9, MMP13, TIMP1, VEGF expression and decrease in MMP3. Chung et al.[28] found increased expression of *MMP9* and *IL6* genes in diabetics. The authors suggested that this difference may be one of the explanations for increased repair failure in diabetic patients.

Our group, in 2017, described through a Reverse transcription polymerase chain reaction quantitative real time (qRT-qPCR) study, with a normalized sample using the *HPRT1, BPT* and *ACTB* genes, the decrease in *MMP1* expression, *MMP9* and *MMP13* and the increase in *IMPT3* in individuals with injury in relation to controls.[29] In another study, the presence of polymorphisms related to *MMP1, MMP-2, MMP-3, MMP-9, MMP-13, TIMP-1, TNC* and *COL5A1* genes in patients with RCI was also observed. These authors found 15 SNPs of the *TNC* gene and they were significantly associated with degenerative lesions.[30]

Ahn et al.[31] evaluated 14 patients who underwent repair and concluded that negative regulation of inflammatory response genes and positive regulation of cell differentiation genes at the time of surgery are related to rotator cuff healing.

Treviño et al.[32] evaluated the expression of proteases (catepsins and *MMP*) of tendon tissues and supraspinal muscle, in addition to the humeral cartilage of 30 rats after RCI at 3 distinct moments: 1, 3 and 12 weeks. The authors concluded that there is a significant increase in proteases in the three tissues, each with different profiles, and initially the increase in expression in the tendons and posterior in the humeral cartilage.

Lee et al.,[33] in a study with rats, analyzed 39,429 genes and followed changes in their expression after 1 and 4 weeks of injury and identified that rotator cuff rupture induces the expression of specific genes related to aging, apoptosis, atrophy and transport of fatty acids. The authors associated that many genes that are altered may play a role in the tendon degeneration process after the injury. In 2018, our group described that the altered expression of the genes *COL1A1, COL1A2, COL3A1, COL5A1, FN1, TNC, TGFB1,* and *TGFBR1* is involved in the process of degeneration in ruptures of the rotator cuff.[34]

In a systematic review study, Dabija et al. concluded that although previous studies provide preliminary evidence of genetic and family predisposition to RCIs, there is a lack of large genomic studies that can provide more definitive information and guide the early detection of individuals at risk, prophylactic rehabilitation and potential gene therapies and interventions in regenerative medicine.[10]

A more recent study conducted an extensive analysis using Gene Expression Omnibus (GEO) gene expression profile gse93661 and bioinformatics analysis to investigate differentially expressed genes (DEGs) in satellite cells between samples of cases of supraspinal injury and subscapular tendon controls. In total, 551 DEGs were identified, including 272 hyper-regulated DEGs and 279 hypo-regulated DEGs pointing out a number of genes (*GNG13*, *GCG*, *NOTCH1*, *BCL2*, *NMUR2*, *PMCH*, *FFAR1*, *AVPR2*, *GNA14* and *KALRN*) and thus providing clues to speculate that the GNG13/ signaling pathway/calcium is highly correlated with denervation atrophy in the pathological process of RCI. [35]

There is a line of research of our group in which we analyze the difference in gene expression between bursal and articular partial lesions, using genetic ontology system and Next-Generation Sequencing (NGS) platform. The bursal partial lesion proved to be genetically more complex because it presented a higher number of genes identified by NGS, and most genes that showed increased expression were associated with fusion, adhesion or interaction of the cell with the extracellular matrix, while hyperexpression of the *EGLN3* gene, an oxygen saturation sensor tissue and suppression of the *ID1* gene, an important regulator of biological processes including cell growth, senescence, differentiation, apoptosis, angiogenesis and neoplastic transformation. (André Godinho's professional master's thesis, unpublished data).

Finally, in another line of investigation, which seeks to understand whether fatty infiltration (FI) and inflammation slow healing in RCIs, Thankam et al. evaluated miRNAs of patients with and without FI and inflammation and detected 13 miRNAs and 216 genes-targets that interconnect the activated protein kinase (AMPK) metabolic checkpoint and the pathway of the inflammatory molecule TREM-1.[36]

Shoulder instability

Shoulder instability, like other orthopedic conditions, has a possible genetic component. Foëx reported the presence of

recurrent shoulder displacements in three generations of a UK family.[37] Imazato et al.[38] demonstrated that in patients with multidirectional shoulder instability, the collagen fibers of the capsule, muscles and skin are relatively immature, more soluble and with less crosslink than controls.

In a population of Sweden, it was observed that homozygotes with the rare allusion in the rs1800012 polymorphism (on the Sp1 binding site) of the gene encoding collagen chain 1 type 1 (COL1A1) was a protective factor for shoulder instability (N = 126).[39] Collins et al.[40] bringing together the results of caucasoid individuals from Sweden and South Africa, investigated whether this *COL1A1* polymorphism was associated with the risk of cruciate ligament injury, anterior knee instability, shoulder instability and Achilles tendon ruptures. The authors described that the TT genotype was a protective factor against the lesion, when all lesions were combined and compared with control individuals.

Initially, Belangero et al.[41] investigated the expression of the genes *COL1A1*, *COL1A2*, *COL3A1* and *COL5A1* in the anteroinferior region (macroscopically altered) and compared with the anterosuperior region of the glenohumeral capsule of 18 patients with traumatic anterior instability (TAI). They identified reduced expression of *COL5A1* in the upper region. The same authors demonstrated in 2014 that *COL1A1* expression and *COL1A1/COL1A2* ratio were increased in all regions (anterosuperior, anteroinferior and posterior) of the capsule, in patients with TAI when compared with controls, and this ratio seems to reduce in the anteroinferior region the longer the symptom exists. The ratio between *COL1A1/COL5A1* was also increased in the anteroinferior and posterior region of the capsule.[42] In 2016, they evaluated genes related to the collagen crosslink process and suggested that expression changes in the genes of *TGFB1, TGFBR1, LOX* and *PLOD2* may play a role in shoulder instability.[43] Finally, when evaluating the expression of genes encoding proteins of the extracellular matrix *(COMP, FN1, TNC* and *TNXB*) they found higher expression of *TNC* and *FN1* in the anteroinferior part of the capsule and *FN1* is directly correlated with the duration of symptoms and with recurrent displacements in relation to controls.[44] *COMP* expression was reduced, and may be associated with the integrity of the capsule after shoulder dislocation, particularly in the portion of the macroscopically affected.

Frozen Shoulder

The positive family history of frozen shoulder (FS) is described in 9.5 up to 20% of the cases,[45,46] the prevalence calculated in a twin study is 11.6% and the heritability estimate is of 42%.[47] The idiopathic aspect of the lesion and studies such as the one that reports the case of monozygotic siblings with bilateral frozen shoulder developed at the same time[48] favor the genetic propensity of affected individuals theory. In addition, other data that reinforce the probable genetic influence of complex patterns (gene-environment interaction) of the FS is the curious association with Dupuytren disease (DD) which is a complex, multifactorial disease, with a strong known genetic component.[49]

There is great histological similarity between the fibroproliferative processes of the two diseases,[50] and the association between fibrotic conditions (frozen shoulder and DD), joint stiffness and total arthroplasties has been reported. Fibrotic conditions showed heritability of 28%. These findings are suggestive of a genetic influence on a common process of underlying disease that affects connective tissues.[51] The increased expression of *TGFB* and *TGFBR1* and decreased *MMP2* levels in the capsular tissue of affected shoulders were demonstrated.[52] In agreement, Bunker et al.[53] also demonstrated a decrease in mRNA expression of *MMP1* and *MMP2,* similar to DD.

Our group detected in the capsule of eight FS operated patients, compared with controlling individuals, that this hyperregulation of *TGFBR1* was directly related to the duration of symptoms suggesting that TGFB signaling should be involved in the development of the disease. In addition, an increase in the expression of MRNA of *FN1* and *TNC* mRNA has been demonstrated in the affected capsule fragments that may be involved in the process of inflammation and migration of fibroblasts.[54] Lubis et al.[52] investigated serum levels of MMPs, TIMPs and TGF11 in FS and normal individuals using the enzyme-linked immunosorbent assay (ELISA) method. Baseline levels of MMP1 and MMP2 were significantly lower, while TIMP1, TIMP2 and TGF levels[1] were significantly higher in the FS group, with findings similar to the fibroproliferative disorders in DD.[9] These deficiencies in the production of MMP1 may reflect an altered capacity for local tissue remodeling.[55]

Kabbabe et al.[56] used the quantitative polymerase chain reaction (PCR) technique to show increased expression levels of *MMP3* and its role as a fibrogenic mediator in the FS compared to the control group. Xu et al.[57] concluded that the increased expression of the *MMP3* rs650108 variant was significantly associated with FS susceptibility in a Chinese Han population.

In 2017, Chen et al.[58] studied IL-11,MMP3, TGF-1,and GDF5 SNPs in a small Chinese population and found that the FS genotype of IL-11143627 polymorphism was associated with lower FS risk compared with genotype TT ($p = 0.022$) and that serum IL-1was expressed at a significantly higher level when compared with the control group ($p < 0.001$).

In addition, our group analyzed 18 polymorphisms in genes encoding proteins involved in the homeostasis of the extracellular matrix of the capsule and the signaling pathway of TGF1. Genes encoding collagens (*COL1A1, COL5A1*), glycoproteins (*FN1, TNC*) genes involved in signaling the transformer growth factor and its receptor (*TGFB1, TGFBR1*), metalloproteinases (*MMP2, MMP3, MMP9, MMP13*) and tissue inhibitor of MMP2 (*TIMP2 rs2277598*) were selected. While in men the association of *TGFBR1* and *TGFBR1* polymorphisms was pointed out, in women *MMP2* and *MMP9* metalloproteinases were pointed out as risk factors for development of FS. Only *MMP13* was related to both genders.[59] MMP13, collagenase metalloproteinase, divide the main structural component of cartilage, type II collagen, thus effecting irreversible loss of Extracellular matrix (ECM) architecture and function. The expression of MMP

collagenase was significantly elevated in the nodule tissue sample of patients operated for DD, where high collagen turnover occurs; however, high levels of TIMP1 blocking the action of MMP13 in the breakdown of collagen was appointed as possibly responsible for the process of contracture and fibrosis in these individuals.[60]

Perspectives

The era of individual genetics has grown exponentially in recent years. Along with the growing number of publications, there is great frustration due to conflicting results, the expectation of clinical application of the results and the lack of replication of the findings, mainly due to the low statistical power and the high rate of false-positives. In addition, diseases are controlled by the sum of expression of various genes, but each with small effect. It is still necessary to catalog different shoulder-related polymorphisms, since the genomic profile will allow the defining of a database of genetic markers that may contribute to the risk of diseases. Thus, knowledge of molecular bases can help in the development of better prevention, diagnosis and treatment tools.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. Nature 2001;409(6822):860–921
2 Leal MF, Belangero SI. Variantes genéticas nas lesões do sistema musculoesquelético em atletas. In: Cohen M, Abdalla RJ. Lesões nos Esportes: Diagnóstico, Prevenção e Tratamento. 2a. ed. Rio de Janeiro: Revinter; 2015:5–56
3 Frank CB. Ligament structure, physiology and function. J Musculoskelet Neuronal Interact 2004;4(02):199–201
4 Mitchell AL, Schwarze U, Jennings JF, Byers PH. Molecular mechanisms of classical Ehlers-Danlos syndrome (EDS). Hum Mutat 2009;30(06):995–1002
5 Chiquet-Ehrismann R, Tucker RP. Tenascins and the importance of adhesion modulation. Cold Spring Harb Perspect Biol 2011;3(05): a004960
6 Dallas SL, Sivakumar P, Jones CJ, et al. Fibronectin regulates latent transforming growth factor-beta (TGF beta) by controlling matrix assembly of latent TGF beta-binding protein-1. J Biol Chem 2005; 280(19):18871–18880
7 Badalamenti MA, Sampson SP, Hurst LC, Dowd A, Miyasaka K. The role of TGF-beta in Dupuytren's disease. J Hand Surg Am 1996;21 (02):210–215
8 Wahl SM, Costa GL, Mizel DE, Allen JB, Skaleric U, Mangan DF. Role of transforming growth factor beta in the pathophysiology of chronic inflammation. J Periodontol 1993;64(5, Suppl)450–455
9 Ulrich D, Hrynyschyn K, Pallua N. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in sera and tissue of patients with Dupuytren's disease. Plast Reconstr Surg 2003; 112(05):1279–1286
10 Dabija DI, Gao C, Edwards TL, Kuhn JE, Jain NB. Genetic and familial predisposition to rotator cuff disease: a systematic review. J Shoulder Elbow Surg 2017;26(06):1103–1112
11 Harvie P, Ostlere SJ, Teh J, et al. Genetic influences in the aetiology of tears of the rotator cuff. Sibling risk of a full-thickness tear. J Bone Joint Surg Br 2004;86(05):696–700
12 Gwilym SE, Watkins B, Cooper CD, et al. Genetic influences in the progression of tears of the rotator cuff. J Bone Joint Surg Br 2009; 91(07):915–917
13 Tashjian RZ, Farnham JM, Albright FS, Teerlink CC, Cannon-Albright LA. Evidence for an inherited predisposition contributing to the risk for rotator cuff disease. J Bone Joint Surg Am 2009;91 (05):1136–1142
14 Tashjian RZ, Saltzman EG, Granger EK, Hung M. Incidence of familial tendon dysfunction in patients with full-thickness rotator cuff tears. Open Access J Sports Med 2014;5:137–141
15 Gumina S, Villani C, Arceri V, et al. Rotator Cuff Degeneration: The Role of Genetics. J Bone Joint Surg Am 2019;101(07):600–605
16 Riley GP, Curry V, DeGroot J, et al. Matrix metalloproteinase activities and their relationship with collagen remodelling in tendon pathology. Matrix Biol 2002;21(02):185–195
17 Lo IK, Boorman R, Marchuk L, Hollinshead R, Hart DA, Frank CB. Matrix molecule mRNA levels in the bursa and rotator cuff of patients with full-thickness rotator cuff tears. Arthroscopy 2005; 21(06):645–651
18 Lo IK, Marchuk LL, Hollinshead R, Hart DA, Frank CB. Matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase mRNA levels are specifically altered in torn rotator cuff tendons. Am J Sports Med 2004;32(05):1223–1229
19 Shindle MK, Chen CC, Robertson C, et al. Full-thickness supraspinatus tears are associated with more synovial inflammation and tissue degeneration than partial-thickness tears. J Shoulder Elbow Surg 2011;20(06):917–927
20 Shirachi I, Gotoh M, Mitsui Y, et al. Collagen production at the edge of ruptured rotator cuff tendon is correlated with postoperative cuff integrity. Arthroscopy 2011;27(09):1173–1179
21 Robertson CM, Chen CT, Shindle MK, Cordasco FA, Rodeo SA, Warren RF. Failed healing of rotator cuff repair correlates with altered collagenase and gelatinase in supraspinatus and subscapularis tendons. Am J Sports Med 2012;40(09):1993–2001
22 Gotoh M, Mitsui Y, Shibata H, et al. Increased matrix metalloprotease-3 gene expression in ruptured rotator cuff tendons is associated with postoperative tendon retear. Knee Surg Sports Traumatol Arthrosc 2013;21(08):1807–1812
23 Motta GdaR, Amaral MV, Rezende E, et al. Evidence of genetic variations associated with rotator cuff disease. J Shoulder Elbow Surg 2014;23(02):227–235
24 Teerlink CC, Cannon-Albright LA, Tashjian RZ. Significant association of full-thickness rotator cuff tears and estrogen-related receptor-β (ESRRB). J Shoulder Elbow Surg 2015;24(02):e31–e35 Erratum in: J Shoulder Elbow Surg 2016;25(5):864
25 Tashjian RZ, Granger EK, Farnham JM, Cannon-Albright LA, Teerlink CC. Genome-wide association study for rotator cuff tears identifies two significant single-nucleotide polymorphisms. J Shoulder Elbow Surg 2016;25(02):174–179
26 Assunção JH, Godoy-Santos AL, Dos Santos MCLG, Malavolta EA, Gracitelli MEC, Ferreira Neto AA. Matrix Metalloproteases 1 and 3 Promoter Gene Polymorphism Is Associated With Rotator Cuff Tear. Clin Orthop Relat Res 2017;475(07):1904–1910
27 Sejersen MH, Frost P, Hansen TB, Deutch SR, Svendsen SW. Proteomics perspectives in rotator cuff research: a systematic review of gene expression and protein composition in human tendinopathy. PLoS One 2015;10(04):e0119974
28 Chung SW, Choi BM, Kim JY, et al. Altered Gene and Protein Expressions in Torn Rotator Cuff Tendon Tissues in Diabetic Patients. Arthroscopy 2017;33(03):518–526.e1
29 Leal MF, Caires Dos Santos L, Martins de Oliveira A, et al. Epigenetic regulation of metalloproteinases and their inhibitors in rotator cuff tears. PLoS One 2017;12(09):e0184141
30 Kluger R, Burgstaller J, Vogl C, Brem G, Skultety M, Mueller S. Candidate gene approach identifies six SNPs in tenascin-C (TNC) associated with degenerative rotator cuff tears. J Orthop Res 2017;35(04):894–901

31 Ahn JO, Chung JY, Kim DH, Im W, Kim SH. Differences of RNA Expression in the Tendon According to Anatomic Outcomes in Rotator Cuff Repair. Am J Sports Med 2017;45(13):2995–3003
32 Treviño EA, McFaline-Figueroa J, Guldberg RE, Platt MO, Temenoff JS. Full-thickness rotator cuff tear in rat results in distinct temporal expression of multiple proteases in tendon, muscle, and cartilage. J Orthop Res 2019;37(02):490–502
33 Lee YS, Kim JY, Kim HN, Lee DW, Chung SW. Gene Expression Patterns Analysis in the Supraspinatus Muscle after a Rotator Cuff Tear in a Mouse Model. BioMed Res Int 2018;2018:5859013
34 Santoro Belangero P, Antônio Figueiredo E, Cohen C, et al. Changes in the expression of matrix extracellular genes and TGFB family members in rotator cuff tears. J Orthop Res 2018;36(09): 2542–2553
35 Ren YM, Duan YH, Sun YB, Yang T, Tian MQ. Bioinformatics analysis of differentially expressed genes in rotator cuff tear patients using microarray data. J Orthop Surg Res 2018;13(01):284
36 Thankam FG, Boosani CS, Dilisio MF, Gross RM, Agrawal DK. Genes interconnecting AMPK and TREM-1 and associated microRNAs in rotator cuff tendon injury. Mol Cell Biochem 2019;454(1-2):97–109
37 Foëx BA. Three generations of recurrent dislocated shoulders. Emerg Med J 2001;18(02):148–149
38 Imazato Y. [Etiological considerations of the loose shoulder from a biochemical point of view–biochemical studies on collagen from deltoid and pectoral muscles and skin]. Nippon Seikeigeka Gakkai Zasshi 1992;66(10):1006–1015
39 Khoschnau S, Melhus H, Jacobson A, et al. Type I collagen alpha1 Sp1 polymorphism and the risk of cruciate ligament ruptures or shoulder dislocations. Am J Sports Med 2008;36(12):2432–2436
40 Collins M, Posthumus M, Schwellnus MP. The COL1A1 gene and acute soft tissue ruptures. Br J Sports Med 2010;44(14):1063–1064
41 Belangero PS, Leal MF, de Castro Pochini A, Andreoli CV, Ejnisman B, Cohen M. Profile of collagen gene expression in the glenohumeral capsule of patients with traumatic anterior instability of the shoulder. Rev Bras Ortop 2014;49(06):642–646
42 Belangero PS, Leal MF, Figueiredo EA, et al. Gene expression analysis in patients with traumatic anterior shoulder instability suggests deregulation of collagen genes. J Orthop Res 2014;32 (10):1311–1316
43 Belangero PS, Leal MF, Cohen C, et al. Expression analysis of genes involved in collagen cross-linking and its regulation in traumatic anterior shoulder instability. J Orthop Res 2016;34 (03):510–517
44 Belangero PS, Leal MF, Figueiredo EA, et al. Differential expression of extracellular matrix genes in glenohumeral capsule of shoulder instability patients. Connect Tissue Res 2016;57(04):290–298
45 Cohen C, Ejnisman B. Epidemiology of frozen shoulder. In: Itoi E, Arce G, Bain GI, Diercks RL, Guttmann D, Imhoff AB, et al. Shoulder stiffness. Berlin: Springer Verlag; 2015:21–30
46 Hand GC, Athanasou NA, Matthews T, Carr AJ. The pathology of frozen shoulder. J Bone Joint Surg Br 2007;89(07):928–932
47 Hakim AJ, Cherkas LF, Spector TD, MacGregor AJ. Genetic associations between frozen shoulder and tennis elbow: a female twin study. Rheumatology (Oxford) 2003;42(06):739–742
48 Hirschhorn P, Schmidt JM. Frozen shoulder in identical twins. Joint Bone Spine 2000;67(01):75–76
49 Larsen S, Krogsgaard DG, Aagaard Larsen L, Iachina M, Skytthe A, Frederiksen H. Genetic and environmental influences in Dupuytren's disease: a study of 30,330 Danish twin pairs. J Hand Surg Eur Vol 2015;40(02):171–176
50 Bunker TD, Anthony PP. The pathology of frozen shoulder. A Dupuytren-like disease. J Bone Joint Surg Br 1995;77(05): 677–683
51 Williams FM, Kalson NS, Fabiane SM, Mann DA, Deehan DJ. Joint Stiffness Is Heritable and Associated with Fibrotic Conditions and Joint Replacement. PLoS One 2015;10(07):e0133629
52 Lubis AM, Lubis VK. Matrix metalloproteinase, tissue inhibitor of metalloproteinase and transforming growth factor-beta 1 in frozen shoulder, and their changes as response to intensive stretching and supervised neglect exercise. J Orthop Sci 2013; 18(04):519–527
53 Bunker TD, Reilly J, Baird KS, Hamblen DL. Expression of growth factors, cytokines and matrix metalloproteinases in frozen shoulder. J Bone Joint Surg Br 2000;82(05):768–773
54 Cohen C, Leal MF, Belangero PS, et al. The roles of Tenascin C and Fibronectin 1 in adhesive capsulitis: a pilot gene expression study. Clinics (São Paulo) 2016;71(06):325–331
55 Brown ID, Kelly IG, McInnes IB. Detection of matrix metalloproteinases in primary frozen shoulders. J Bone Joint Surg Br 2008;90 (Suppl 2):364
56 Kabbabe B, Ramkumar S, Richardson M. Cytogenetic analysis of the pathology of frozen shoulder. Int J Shoulder Surg 2010;4(03): 75–78
57 Xu Q, Gai PY, Lv HL, Li GR, Liu XY. Association of MMP3 genotype with susceptibility to frozen shoulder: a case-control study in a Chinese Han population. Genet Mol Res 2016;15(01):. Doi: 10.4238/gmr.15017228
58 Chen W, Meng J, Qian H, et al. A Study of *IL-1β*, *MMP-3*, *TGF-β1*, and *GDF5* Polymorphisms and Their Association with Primary Frozen Shoulder in a Chinese Han Population. BioMed Res Int 2017; 2017:3681645
59 Cohen C, Leal MF, Loyola LC, et al. Genetic variants involved in extracellular matrix homeostasis play a role in the susceptibility to frozen shoulder: A case-control study. J Orthop Res 2019;37 (04):948–956
60 Johnston P, Chojnowski AJ, Davidson RK, Riley GP, Donell ST, Clark IM. A complete expression profile of matrix-degrading metalloproteinases in Dupuytren's disease. J Hand Surg Am 2007;32 (03):343–351