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.
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. 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.

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. 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. 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.

Additionally, other collagens, collagen synthesis modulator genes (TGFβ, TGFβ1), metalloproteinases, proteoglycans that may be associated with fibrils and glycoproteins – for example, fibronectin (FN) and tenasin C (TNC), which act in the modulation of TGFβ and in the tendon repair process by promoting migration and adherence of fibroblasts to fibrils. Cytokines, such as TGFβ1 and its receptors, can play a key role in inflammatory and fibrotic processes, regulating various ECM proteins, including collagens, FN1 and TNC. 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.

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. These enzymes are classified based on their substrate preference, including collagenases (e.g., MMP1 and MMP13), stromes (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. Studies in the literature show that siblings of individuals with RCI are more likely to develop complete injury and risk of being symptomatic. Recently, in a study with 33 pairs of elderly twins (17 monozygotics and 16 dizygotic), Gumina et al. 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. evaluated 10 patients and 24 controls and found decreased expression of the MMP2, MMP9, MMP13 genes.

Lo et al. 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 aggrecan, in addition to inhibition of the expression of decorine.

Shindle et al. found increased expression of MMP9, MMP13, COX2 and COL1A1 as well as decreased expression of iNOS, VEGF, COL3A1 and bigican. Shirachi et al. analyzed the expression of COL1A1 and COL3A1 at the edge of the lesion of the supraspinous 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. 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. Gottho et al. 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, ESR8B, FGF3, FGF10 and FGFR1. The authors also concluded that female and white gender are the main predictors of this type of injury. Confirming these findings, mutations of the ESR8B 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). It is noteworthy that this series of cases did not distinguish patients with traumatic and degenerative injuries.

Tashjian et al. 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. Sejersen et al. 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. 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 TIMP3 in individuals with injury in relation to controls. 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.

Ahn et al. 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. evaluated the expression of proteases (cathepsins 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. 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, FNI, TNC, TGFBI, and TGFBR1 is involved in the process of degeneration in ruptures of the rotator cuff.

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.

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 (NGN13, GCG, NOTCH1, BCL2, NMUR2, PMCH, FFAR1, AVPR2, GNA14 and KALRN) and thus providing clues to speculate that the NGN13 signaling pathway/calcium is highly correlated with denervation atrophy in the pathological process of RCI.

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.

**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. Imazato et al. 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). Collins et al. 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. investigated the expression of the genes COL1A1, COL1A2, COL3A1 and COL5A1 in the anterosuperior 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. In 2016, they evaluated genes related to the collagen crosslink process and suggested that expression changes in the genes of TGF1, TGFBR1, LOX and PLOD2 may play a role in shoulder instability. 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. 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, the prevalence calculated in a twin study is 11.6% and the heritability estimate is of 42%. The idiopathic aspect of the lesion and studies such as the one that reports the case of monzygotic siblings with bilateral frozen shoulder developed at the same time 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. There is great histological similarity between the fibroproliferative processes of the two diseases, 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. The increased expression of TGF and TGFBR1 and decreased MMP2 levels in the capsular tissue of affected shoulders were demonstrated. In agreement, Bunker et al. 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 TGF 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. Lubis et al. 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 were significantly higher in the FS group, with findings similar to the fibroproliferative disorders in DD. These deficiencies in the production of MMP1 may reflect an altered capacity for local tissue remodeling.

Kabbabe et al. 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. 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. studied IL-11, MMP3, TGF-1, and GDF5 SNPs in a small Chinese population and found that the FS genotype of IL-1143627 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, COL3A1), glycoproteins (FN1, TNC) genes involved in signaling the fibroproliferative growth factor and its receptor (TGFBR1, 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. 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 contraction 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.

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