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REVIEW

Genetic polymorphism on the flexibility of elite rhythmic gymnasts: State of art

Carla C. Silva[a,*], Lucilene F. Silva[b], Camila R. Santos[c], Tamara B.L. Goldberg[d], Solange P. Ramos[e], Emerson J. Venancio[f]

[a] *Profa. Adjunta ao Departamento de Educação Física, Universidade Estadual do Norte do Paraná, Grupo de Estudos em Adaptações Biológicas do Treinamento Infantil-GEABTI, Jacarezinho, PR, Brazil*
[b] *Curso de Educação Física, Universidade Estadual do Norte do Paraná, Grupo de Estudos em Adaptações Biológicas do Treinamento Infantil-GEABTI, Jacarezinho, PR, Brazil*
[c] *Diretoria de Operações Acadêmicas da Graduação Presencial, Ciências Biológicas e Saúde, Tutoria eletrônica, Universidade do Norte do Paraná, Londrina, PR, Brazil*
[d] *Postgraduate Program in Gynecology, Obstetrics, and Mastology, Discipline of Adolescent Medicine, Department of Pediatrics, Botucatu Medicine School, UNESP, São Paulo State University, Brazil*
[e] *Departamento de Histologia, Centro de Ciências Biológicas, Universidade Estadual de Londrina, PR, Brazil*
[f] *Departamento de Ciências Patológicas, Centro de Ciências Biológicas, Universidade Estadual de Londrina, PR, Brazil*

Abstract   Rhythmic gymnastics has been an Olympic sport since 1984, however, there are relatively few studies about this sport. In order to understand whether genetic predisposition could play a role in defining the flexibility phenotype in rhythmic gymnastics, the purpose of this study was to review the current literature and systematically identify common polymorphisms linked to genes correlated with joint mobility in elite rhythmic gymnastics. Systematic computerized searches were performed from 1950 to 2017 in the following databases: Medline, Embase, Cinahl, Lilacs, SPORTDiscus, Web of Science, Scopus and the Cochrane Central. Although the search initially identified 9761 studies, after removing duplicates and excluding by title and abstract, only 10 studies demonstrated potential to be included. After reading of full-texts, 9 studies were entered in the qualitative synthesis, thus only 1 study was eligible for this systematic review. The results of Tringali's study demonstrated that the COL5A1 CT genotype was linked to high joint mobility and to the occurrence of genu recurvatum. From this systematic review, further investigations are suggested to confirm the results of involving genes related to physiological and anthropometric determinants of rhythmic gymnastics performance.
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* Corresponding author.
E-mail address: ccsilva@uenp.edu.br (C.C. Silva).

Polimorfismo genético en la flexibilidad de gimnastas rítmicos de la élite: estado de arte

Resumen   La gimnasia rítmica ha sido un deporte olímpico desde 1984, sin embargo, hay relativamente pocos estudios sobre este deporte. Para entender si la predisposición genética podría desempeñar un papel en la definición del fenotipo de la flexibilidad en gimnasia rítmica, el propósito de este estudio era revisar la literatura actual e identificar sistemáticamente los polimorfismos comunes ligados a genes correlacionados con la movilidad articular en la gimnasia rítmica de élite. Se realizaron búsquedas sistemáticas computarizadas desde 1950 a 2017 en las siguientes bases de datos: MEDLINE, EMBASE, CINAHL, LILACS, SPORTDiscus, Web of Science, Scopus y la Central Cochrane. Aunque la búsqueda de la base de datos identificó inicialmente 9.761 estudios, después de quitar duplicados y de excluir por título y resumen, solamente 10 estudios demostraron el potencial que se incluirá. Después de la lectura de textos completos, se introdujeron 9 estudios en la síntesis cualitativa, por lo que solo un estudio fue elegible para esta revisión sistemática. Los resultados del estudio de Tringali demostraron que el genotipo COL5A1 CT fue ligado a la alta movilidad común y a la ocurrencia del *genu recurvatum*. A partir de esta revisión sistemática, se sugieren investigaciones adicionales para confirmar los resultados de la participación de genes relacionados con los determinantes fisiológicos y antropométricos del rendimiento de la gimnasia rítmica.

Introduction

The gymnastics modalities, artistic, rhythmic, trampoline, and tumbling are recognized for involving highly specialized strength, endurance, speed, agility, balance, power, and flexibility. All these physical abilities play a role in the success of a competitive gymnast.[1-3] The notorious levels of flexibility are the single greatest discriminator of gymnastics from other sports, especially in rhythmic gymnasts.[1,3-7] Moreover, the high-level of physical performance in rhythmic gymnastics is influenced by the association between numerous motor skills and anthropometric factors.[5,6] This sport is characterized by rigid technical movements such as pivots, balance, jumps, and poise,[5,8,11,12] and generally, in competitive routines that last about 60–90 s, requires the use of a considerable degree of flexibility and velocity in a high-intensity effort with dexterous manipulation of the associated apparatus.[5]

In fact, results in rhythmic gymnastics competitions depend on a large number of complex components such as technical, artistic, and aesthetic elements, and extreme ranges of motion,[1] and it has been postulated by some authors that these factors are influenced by genetics aspects.[7,9,11-13]

The recognition of factors, genetic and/or environmental, to identify early talent is especially important for early specialization sports in which athletes make their appearance at the highest competitive levels at a relatively young age, such as rhythmic gymnastics.[2] Thus, in recent decades, the relationship between elite sports performance and genetic predisposition has been widely explored.[2,14-16] Genetic analysis is useful for talent identification in rhythmic gymnastics as it could identify athletes more predisposed to some anthropometric features and flexibility.[7,17] In particular, extreme range of motion among rhythmic gymnastics has always been a main criterion in selection tests and talent identification.[1] Thereby, the identification of polymorphisms related to flexibility may contribute in the selection of elite athletes, facilitating the mechanism used to identify qualified girls at early ages[18] when the selection of athletes usually occurs, commencing around the age of 6 years.[2]

Previous studies have described polymorphisms within the COL5A1 gene, related to generalized joint hypermobility,[11,19] and the possible influence of the variants of the ACNT3 gene on the flexibility of ballet dancers.[9] However, there are few studies regarding which genetic factors may influence the sports performance of rhythmic gymnastics, specifically the outcome related to flexibility.[7] Thus, in order to understand whether genetic predisposition could play a role in defining the flexibility phenotype in elite rhythmic gymnastics, the purpose of this study was to review the current literature and systematically identify common polymorphisms linked to genes correlated with joint mobility in elite rhythmic gymnastics.

Methods

This systematic review followed the recommendations of the PRISMA Statement.[20] The protocol for the review was registered with PROSPERO (International Prospective Register for Systematic Review; reference CRD42017057333).

Search

A systematic review was originally completed on 29th December 2017 and later updated on 02nd May 2018 in the following databases: MEDLINE, Embase, LILACS (Latin American and Caribbean Health Science Literature Database), SciELO (Scientific Electronic Library Online), SPORTDiscus,

Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). Furthermore, the 'grey area' was consulted (references of included manuscripts, thesis, and abstracts). The strategy was specific for each of the electronic databases, composed of the targets: population, exposures, and outcome. The search strategy was formulated with the following keywords, inserted both in isolation and combined: athletes, female (Population), genotypes, gene, polymorphisms, heritability (Exposures), flexibility, joint mobility, range of motion (Outcome). There were no language restrictions or specific periods of publication.

Inclusion and exclusion criteria

Participants/population
The participants included from the eligible studies were only female rhythmic gymnastics athletes, regardless of their competitive levels, length of experience, age, or the size of the sample. Hereinafter, studies with athletes involved in other types of gymnastics, such as, artistic gymnastics, aerobic, acrobatic, or artistic activities such as ballet dancers or similar were excluded. In addition, studies with participants who had diseases, injuries, or were in rehabilitation were also rejected.

Exposures
In this review, studies related to any type of polymorphism gene that affects joint mobility associated with performance of rhythmic gymnastics were included. Studies with polymorphisms involving other motor capacities, not flexibility, such as strength, velocity, or balance were excluded from the qualitative synthesis.

Outcomes
The definition of the tests or the association for the comparison of range of motion with the gene, or the form of extraction of genetic DNA did not form part of the requirements for inclusion of studies.

Study designs

Quantitative experimental studies, such as cross-sectional or longitudinal studies, and case control studies were considered. Controls groups were not necessary, only that the population consisted of rhythmic gymnastics athletes, where evaluation of the performance of flexibility was compulsory, through testing or physical association, related to the genetic structure.

Study selection

For inclusion in the current study, two authors (CRS, LFS) screened the search results for potentially eligible studies. When titles and abstracts suggested that a study was potentially eligible for inclusion, a copy of the full text of the manuscript was obtained. Disagreements between the two authors regarding a study's eligibility were solved by discussion or, when necessary, by a third author (CCS). The aim was to identify investigations that declared whether there are genetic polymorphisms which affect joint mobility and, if this is associated with performance in female rhythmic gymnastics.

Data extraction and categorization

The following information was extracted from the studies considered eligible: Author, year, sample, gene/polymorphism, available performance of flexibility, results, and conclusion. All collected data were entered in a qualitative analysis table for comparison of the results of the selected studies.

Quality assessment

Risk of bias was evaluated using a modified version of the Newcastle-Otawa-Scale (NOS), previously used by Perera et al.[21] The risk of bias was performed only in manuscripts included in a qualitative synthesis. Agreement was achieved between two researchers (CCS and CRS). The NOS contained four domains of risk assessment. In each domain the scale measures the likelihood of bias with four possible scores ranging from 0 to 3, representing high and low risk of bias, respectively. The domains were as follows: selection bias, performance bias, detection bias, and information bias.

Statistical analysis

The Kappa coefficient was calculated using SPSS 20 (Chicago, IL, USA) to assess the agreement among judges for risk of bias of the included studies.

Results

A PRISMA flow diagram is presented in Fig. 1. The original search yielded 9761 studies of which, after exclusion of duplicates ($n = 2169$) the number of papers was 7592. Subsequently, through analysis of titles and abstracts, 7582 papers were removed. The main reasons for exclusion of titles were the studies assessed other physical capacities and did not involve the performance of flexibility, or the population included individuals with diseases, or other sporting modalities.

In total, 10 manuscripts were included in this review in order to better understand the background of the literature and answer the main objective of this study. After reading, only one manuscript was considered eligible considering the aim of this systematic review, hence, the only study included in the qualitative synthesis was published by Tringali et al. in 2014.[7]

The study by Tringali et al.[7] had a design that was especially focused on rhythmic gymnastics and the relationship between genetic aspects and flexibility. The researchers investigated the ratio of the frequencies of alleles and genotypes from ADRB2 and FTO genes in relation to body mass, ACTN3 and ACE genes with explosive strength, and the COL5A1 gene with joint mobility. The results demonstrated that high-level rhythmic gymnasts constituted a genetically selected population, demonstrating a higher frequency of ADRB2 (G allele) and FTO (A allele) linked to a low body mass index and low fat mass. With regard to the phenotype
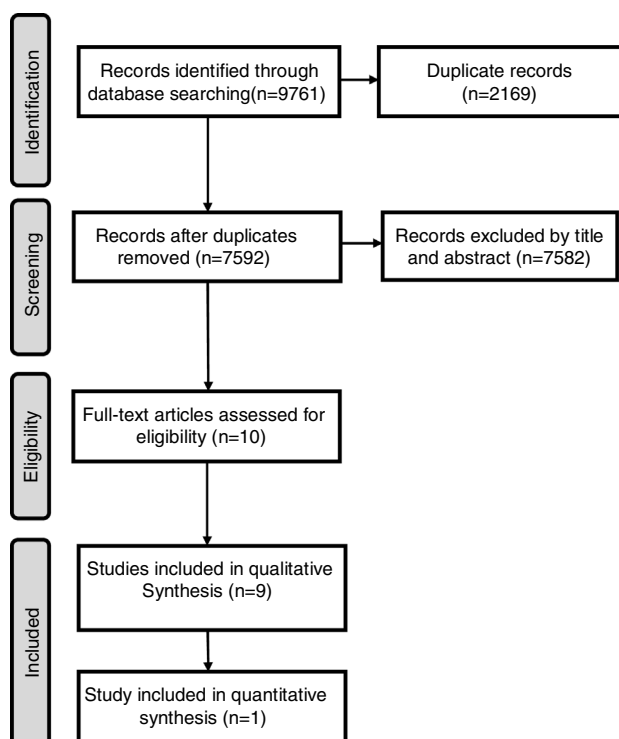
Figure 1 Diagram of the selection of eligible trials from all identified citation.
From Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group.[20]

of explosive force, this study analyzed two polymorphisms, the ACTN3 and ACE genes. The results did not demonstrate any connection between these polymorphisms and explosive force in high-level rhythmic gymnasts. Finally, although the COL5A1 CT genotype was linked to high joint mobility and the occurrence of *genu recurvatum*, it was also linked to a higher incidence of injuries. The authors concluded that high-level performance in rhythmic gymnastics could be positively affected by specific gene variants on the phenotype.

These results are important since they signal the way forward for additional research with recognition that genetic analysis could be useful for talent identification in rhythmic gymnastics as it could indicate athletes more predisposed to some anthropometrical features and/or flexibility. Furthermore, it is important to emphasize that in this quantitative synthesis the risk of bias analysis was performed by two independent researchers using the modified Newcastle-Ottawa-Scale (NOS). The results of the Kappa coefficient were 0.76 and interpreted as good agreement.[22] Even though Tringali et al.[7] performed the only study included in this systematic review, the results of the NOS demonstrated an excellent score, 23 of 24 items, with a low risk of bias. Thus, their conclusions lead the way for new findings.

Additionally, we performed the qualitative synthesis with another 9 manuscripts excluded from the systematic review. The main reasons for the exclusion of these studies were that they did not investigate rhythmic gymnastics, but other modalities of gymnastics and ballet. However, these papers contribute to the identification of research about polymorphism and performance in sports (Table 1).

Through qualitative synthesis of 9 articles we can better compare the outcome and analyze the gene polymorphisms in common in the studies. Although the studies included population samples different from the objective of the literature review, the results of the articles contributed to clarifying and explaining the possible relationships of genes with flexibility.

All included studies were cross-sectional, no intervention took place. To evaluate the performance of flexibility some authors preferred physical tests and others an association of phenotypic characteristics, with or without a control group.

Among the 9 studies in this synthesis, four studies analyzed the COL5A1 gene,[9,11,13,19] three studies investigated the ACTN3 gene,[9,12,23] and three studies analyzed isolated genes. Polymorphism of COL3A1, COL6A1, and COL12A1 genes were studied by O'Connell et al.,[24] while the MMP3 gene was assessed by Posthumus et al.,[25] and ACE and AGTR1 were analyzed by Di Cagno et al.[17]

In the general qualitative results, the COL5A1 gene polymorphism was associated with flexibility performance in active subjects,[11,19] and in the Asian group.[13] However, in the ballerina' group COL5A1 was not associated with any factors of performance.[10] Interestingly, in the same study the XX genotype of the ACTN3 gene showed lower body weight and lower fat-free mass than the RR and RX genotypes ($P < 0.05$). In addition, the means of the sit and reach test for flexibility were lower in the ACTN3 XX genotype of ballerinas than the RR and RX genotypes ($P < 0.05$). The ACNT3 gene polymorphism was further presented in another 2 studies.[12,16] Massidda's study verified that the relationship between the ACTN3 XX genotype and performance was beneficial to skeletal muscle function in generating forceful contractions at high velocity in Italian elite artistic gymnasts, while the results of Kikuchi et al.[12] observed that the RR genotype of ACTN3 R577X in the general Japanese group showed lower sit-and-reach flexibility when compared to the RX and XX genotypes.

Other studies performed analysis with different gene polymorphisms, such as COL3A1, COL6A1, and COL12A1 variants,[24] and a functional variant within the MMP3 gene.[25] The results of both aforementioned studies demonstrated no association of these genotypes with range of motion. Finally, in the qualitative synthesis, Di Cagno et al.[17] performed an evaluation with ACE and AGTR1 polymorphisms in elite rhythmic gymnastics; however these polymorphisms are not related with flexibility, but with endurance performance.

Discussion

To our knowledge, this is the first systematic review to examine the associations of gene variations and range of motion in athletes of rhythmic gymnastics. The main finding of this study was the paucity of evidence, especially as in the quantitative synthesis only one study was found that could be included.[7] However, the review is not weak as a result, mostly as the risk of bias of this study was low and the study recruited a large sample including younger gymnastics ($n = 42$ competitive rhythmic gymnastics; aged 12.8 ± 2.0) compared with a control group ($n = 42$ girls performing sport at recreation level, aged 11.5 ± 5.0 years). The results demonstrated that among athletes, 44% of those

Table 1 Characteristics of excluded studies, selected for qualitative analysis ($n = 9$).

Authors (year)	Sample	Gene	Test of flexibility	Results	Conclusions
Brown, et al. (2011)[19]	325 (204 males and 124 females) subjects, healthy and physically active; aged 18–63 years (young group, aged 18–35 years, older group, aged >=35 years).	COL5A1 gene; rs12722 SNP and TT, TC, or CC genotypes.	SR ROM.	There were no significant genotype interactions with SR ROM. However, the CC genotype is associated with SR ROM in older individuals (>=35 years). Furthermore, sex and the COL5A1 polymorphism explained 22.8% of variance in SR ROM.	The COL5A1 rs12722 SNP interacted significantly with age for SR ROM in an apparently healthy and physically active cohort.
Collins et al. (2009)[11]	119 (83 males; 36 females) subjects, physically active with achilles tendinopathy (TEN group; 34 males and 16 females; mean age 33.9 years); achilles rupture (RUP group; 26 males and 9 females; mean age 46 years); and asymptomatic (CON group; 23 males and 11 females; mean age 49 years).	COL5A1 gene; rs13936 SNP and TT, TC, or CC genotypes; Rs12722 SNP and TT, TC, or CC genotypes; Rs3196378 SNP and AA, AC, or CC genotypes; rs11103544 TT, TC, or CC genotypes.	SR and SLR ROM.	SR and SRL ROM similar between TEN, RUP, and CON. TC genotype from rs12722 polymorphism less flexible than TT and CC genotypes. The factors contributing significantly to SR and SRL ROM were weight, age, and the COL5A1 rs12722 SNP.	The COL5A1 rs12722 SNP interacted significantly with age and weight for ROM.
Di Cagno et al. (2013)[17]	51 rhythmic gymnasts. 28 elite gymnasts, (mean age 21 ± 7.6 years) and 23 middle level (mean age 17 ± 10.9 years). Furthermore, data of 222 subjects of Italian population and 72 subjects of European population from Rajeevan et al., 2003 were used.	ACE gene; rs4646994 SNP and II, ID, or DD genotypes; AGTR1 gene; rs5186 SNP and AA, AC, or CC genotypes.	Not applied.	The ACE D allele was more frequent in elite athletes than in the Italian population ($x^2 = 4.07$, $P = 0.04$). DD genotype was more frequent in elite athletes than in middle level athletes. There were no significant differences in the AGTR1 rs5186 SNP between the middle level and elite athletes.	The ACE D allele could be a contributing factor to high-performance rhythmic gymnastics. It should be considered in athlete development.

Table 1 (*Continued*)

Authors (year)	Sample	Gene	Test of flexibility	Results	Conclusions
Kikuchi et al. (2017)[12]	*Cohort 1*: 776 subjects (208 men and 568 women), age range 23–88 years; *Cohort 2*:1257 subjects (529 men and 728 women), aged 23–87 years.	ACTN3 gene; rs1815739 SNP; TT (XX), TC (XR), or CC (RR) genotypes; T allele encoded a stop codon (X); C allele encoded an arginine (R).	SR ROM – Trunk flexibility test.	In Cohort 1, RR genotype lower SR than those in the RX and XX genotypes even after adjusting for sex, age, and exercise habit as covariates. In Cohort 2, RR genotype lower SR than in RX and XX, but the differences were not significant. Meta-analysis showed that subjects with RR genotype had lower flexibility than RX and XX.	ACTN3 rs1815739 polymorphism is associated with trunk flexibility.
Kim et al. (2014)[9]	300 females (97 ballet dancers and 203 normal females); aged 18 to 39 years.	ACE gene; rs1799572 SNP and II, ID, or DD genotypes; ACTN3 gene; rs1815739 SNP; TT (XX), TC (XR), or CC (RR) genotypes; COL5A1 gene; rs12722 SNP and TT, TC, or CC genotypes.	SR and SLR ROM.	TT (XX) genotype from ACTN3 gene is associated with lower flexibility of ballerinas than TC (XR) and CC (XX) genotypes. Ankle injury is more prevalent in ballerinas with TT (XX) genotype. These ballerinas have a risk of injury in the ankle about 4.7 (95% CI: 1.6–13.4, $P < 0.05$) times more than ballerinas with CC (RR) and CT (RX) – genotypes. Meanwhile, the COL5A1 polymorphism in ballerinas has no association with flexibility and injury risks.	*ACE* and *ACTN3* polymorphism were associated with ballerinas' performance capacity.
Lim et al. (2015)[13]	177 (109 males; 68 females) Korean and Japanese college students. Aged > 18 years.	COL5A1 gene; rs12722 SNP and TT, TC, or CC genotypes.	SR and SLR ROM. In addition, they performed the WBJL.	TT genotype is associated with lower values of SLR in relation to TC or CC genotypes. However, no significant difference was seen in the WBJL among the COL5A1 genotype, but a significant difference was seen in CC genotype when compared to CT (2.99 ± 1.72) or TT (2.70 ± 1.52).	The data indicate an association between the COL5A1 genotypes and SLR ROM in young Asian students.

Table 1 (*Continued*)					
Authors (year)	Sample	Gene	Test of flexibility	Results	Conclusions
Massidda et al. (2009)[16]	88 subjects: 35 Italian elite artistic gymnasts (17 male and 18 female; mean age 10.4 years) and 53 healthy and sedentary subjects (31 male and 22 female). Aged approximately 10.4 years (male: 12.5 ± 5.12years; female: 8.4 ± 1.8 years).	ACTN3 gene; rs1815739 SNP; TT (XX), TC (XR), or CC (RR) genotypes. T allele encoded a stop codon (X); C allele encoded an arginine (R).	Not applied.	ACTN3 XX genotype and X allele frequencies were significantly lower in gymnasts compared to controls. The ACTN3 XX genotype frequency was lower in gymnasts compared to controls, but was only significant for males.	These results suggest that a-actinin-3 is beneficial to skeletal muscle function in generating forceful contractions at high velocity.
O'connell et al. (2013)[24]	350 healthy physically active adults (216 males and 134 females) aged > 18 years.	COL3A1 gene; rs1800255 SNP and GG, GA, or AA genotypes; COL6A1 gene; rs35796750 SNP and TT, TC, or CC genotypes; COL12A1 gene; rs970547 SNP and AA, AG, or GG genotypes.	SR and SLR ROM, and ShTR. Measurements were determined for dominant and non-dominant limbs.	There were no significant genotype interactions with SR ROM, SLR ROM, and ShTR.	No associations between polymorphisms of genes to collagen type III, VI, and XII.
Posthumus et al. (2010)[25]	105 subjects of both genders.	MMP3 gene, rs679620 SNP and AA, AG, and GG genotypes; COL5A1 gene; rs12722 SNP and TT, TC, or CC genotypes. COL5A1 data were from early studies.	SR ROM, and L and R-SLR ROM.	There were no significant genotype interactions with SR ROM or SLR ROM.	No associations between polymorphisms of genes to collagen type V and Matrix Metalloproteinase 3 and SR or SLR ROM.

SR: sit and reach; ROM: range of motion; SLR: passive straight leg raise; WBJR: whole body join laxity; ShTR: total shoulder rotation; L-SLR: left –passive straight leg raise; R-SLR: right – assive straight leg raise; SNP: single nucleotide polymorphism; COL5A1: Collagen Type V Alpha 1 Chain; ACE: angiotensin-converting enzyme; AGTR1: Angiotensin II Receptor Type 1; ACTN3: Actinin Alpha 3; COL3A1: Collagen Type III Alpha 1 Chain; COL6A1: Collagen Type VI Alpha 1 Chain; COL12A1: Collagen Type XII Alpha 1 Chain; MMP3: Matrix Metallopeptidase 3.

carrying the COL5A1 CT genotype, naturally showed *genu recurvatum*. The COL5A1 CT genotype predisposes to joint laxity, and could confer an advantage for rhythmic gymnastics even if it possibly entails a higher risk of injuries, as demonstrated in the results. The 36% of athletes carrying the CT genotype had suffered injuries at least once during their competitive career in comparison to 8% of athletes carrying the TT genotype and none carrying the CC genotype.

Regarding the COL5A1 gene, it is a wide recognized as strongly associated with range of motion,[13] approximately 64–70% of variability of joint range of motion is hereditable,[24,26] mainly through a single nucleotide polymorphism (SNP) rs12722(T/C) within the functional COL5A1. However, there were contradictory results with some studies reporting a positive association between COLA51 and range of motion,[11,13,19] while other studies did not verify an association.[9,25]

Joint hypermobility is consistent with a genetic influence. Hakim et al.[26] observed a significantly greater concordance for joint hypermobility in monozygotic twins when compared with dizygotic twins (60% versus 36%). Thereafter, associations between joint hypermobility, the risk of soft tissue injury, and chronic widespread pain are not uncommon. Collagen gene variants have been reported, associated with anterior cruciate ligament (ACL) injury risk and joint laxity.[27] These authors investigated the genetic variants within the genes coding for collagen types I, V, and XII (COL1A1, COL5A1, and COL12A1) in 124 healthy, recreationally active subjects (50 male, 74 female). The conclusions confirmed that the gene variants previously associated with ACL injury risk were in a large part also associated with joint laxity. On the other hand, genetic collagen disorders, such as Benign Joint Hypermobility Syndrome (BJHS), have been described as possibly being an advantage in certain activities, such as gymnasts and ballet dancers.[28] In the early 1970s Grahame and Jenkins[29] compared the range of joint movements in 53 female dance students from the Royal Ballet School with that of 53 student nurses from Guy's Hospital, London. The study showed that inherent joint laxity was more common among the dancers.[29] Posteriorly, McCormack et al.[28] investigated joint laxity and BJHS in student and professional ballet dancers. The results demonstrated that hypermobility and BJHS were common in male and female dancers compared with controls, suggesting that positive selection on grounds of hypermobility occurs early in a ballet career. However, the limitation of this type of study was that hypermobility was defined by a test score from dynamometer and anthropometric measures without association with genetic aspects.

More recently, Kim et al.[10] studied genetic association flexibility and injury risk with COL5A1 polymorphisms in Korean ballerinas. The results showed that the COL5A1 polymorphism in ballerinas had no association with any factors, including flexibility and injury risks. In the same way, O'Connel et al.[25] also did not observe an association between polymorphisms in COL3A1, COL6A1, and COL12A genes that encode proteins of collagen, which cause connective tissue hypermobility disorders. However, the group assessed by these authors was composed by 350 physically active Caucasian participants, not a specific group, such as ballerinas or gymnasts. These divergent results may be explained as the joint range of motion is a complex phenotype, and is associated with intrinsic and extrinsic factors, including the impact of aging[19] sexual and hormonal factors,[19,27] racial status,[9,27] and several genetic polymorphisms can be associated with range of motion, besides different variants of genes being candidates to explain range of motion.[24,27]

In addition to the COL5A1 genotype, other polymorphisms are also highlighted in the qualitative synthesis of the present study, such as ACTN3 R577X,[9,12,23] which was also described in the study by Tringali et al.[7] in the quantitative synthesis analysis. The ACTN3 R577X polymorphism encodes α-actinin 3 in skeletal muscle fibres, associated with fast and powerful contractions.[30] The general results demonstrated that the ACTN3 XX genotype is also related with low fat-free mass, and a higher risk of ankle-joint injury in ballerinas,[9] besides being associated with trunk flexibility, with the RR genotype showing lower trunk flexibility compared to the RX and XX genotypes in Japanese groups.[12] This same polymorphism (ACTN R577X) was also associated with benefits to skeletal muscle function in generating forceful contractions at high velocity in elite artistic male gymnasts.[23] However, in the main study included in this systematic review,[8] the genotyping of ACTN3 R577X did not appear to be connected with the phenotype of high-level rhythmic gymnasts ($n = 42$).

Among manuscripts inserted in the qualitative synthesis, the only study related to rhythmic gymnastics was the investigation of Di Cagno et al.[17] These authors examined the involvement of ACE and AGTR1 gene polymorphisms in 28 Italian elite rhythmic gymnasts (age range 21 ± 7.6 years), and compared them to 23 middle level rhythmic gymnasts (age range 17 ± 10.9 years). Both polymorphisms studied are related to components of the endocrine renin-angiotensin system which is involved in a variety of cellular functions, including tissue growth and repair, which may also influence motor performance[17] However, there are 2 limitations in this study: the first is these polymorphisms are not related to flexibility or articular hypermobility; and the second is the authors did not apply performance tests to associate with genes.

Finally, despite being a wide systematic review it is appropriate to indicate some limitations of this study. The inclusion of only one study in the quantitative synthesis indicates the need for new investigations. Based on the results of this systematic review, the studies present some contradictory results. For instance no association between COL5A1 and flexibility was observed in Korean ballerinas,[9] while in Tringali's study the same polymorphism demonstrated an association with natural knee hyperextension in the group of rhythmic gymnastics athletes. Although the studies investigated the same polymorphism (rs.12722 of COL5A1 gene), it is important to consider other factors, such as different populations, with the impact of race, and different ways to assess flexibility. These points should be considered when structuring and designing new studies with a focus on this Olympic sport, and preferably with a large sample at different levels of competition and during talent selection.

Conclusions

The findings of this systematic review have many positive implications for the field of research. Primarily, this review

provides a comprehensive synthesis about which gene variation could play a role in the joint mobility of elite rhythmic gymnastics athletes. However, from this review it is possible to recognize that further investigations are required to determine any specific effects of the mutations within the genes that encode the collagen proteins (COL5A1, COL3A1, COL6A1, and COL12A1), and/or to investigate other genes, such as the MMP3 gene, which code for proteins with regulatory roles in maintaining the extracellular matrix, linked with joint hypermobility in rhythmic gymnastics athletes.

Clearly, rhythmic gymnastics is a highly complex sport activity,[7,31] thus, it may not be determined by a single gene, more probably from the interaction of multiple genes, in addition to other non-genetic factors that could explain the different results,[5,14] such as physical training.[4,31] In this perspective, we suggest, from this systematic review, further investigations to confirm the results of Tringali et al.[7] involving genes related to physiological and anthropometric determinants of rhythmic gymnastics performance.

Acknowledgments

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