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The Association between *ACTN3* R577X Polymorphism and Range of Motion: A Systematic Review and Meta-analysis

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ABSTRACT

The R577X polymorphism in the α-actinin-3 gene (*ACTN3*) is associated with muscle strength and power; there is an association between *ACTN3* R577X polymorphism and range of motion (ROM). We examined the effect of the *ACTN3* R577X polymorphism on ROM through meta-analysis and systematic review. Relevant studies published before April 14, 2022 were identified from the PubMed database using the following keywords and Boolean operators: ("flexibility" or "Joint Range of Motion" or "Joint Flexibility" or "Range of motion") and ("ACTN3" or "alpha-actinin 3"). Studies that met the following criteria were included: (1) published in English, (2) included human subjects, (3) provided ROM measurements, and (4) analyzed the *ACTN3* R577X genotype. A total of 2908 participants from seven studies were included in the meta-analysis. The additive genetic model was assessed using a meta-regression model, and dominant and recessive models were analyzed using a random effects model. The ROM in the XX + RX genotype was significantly higher than that in the RR genotype (recessive model: $p < 0.001$), and it increased additively in the order XX > RX > RR (additive model: $p = 0.029$). However, no significant association was observed in the dominant model. These findings further elucidate the association between flexibility and the *ACTN3* R577X genotype.

Introduction

Flexibility parameters, including range of motion (ROM), are an important physical fitness component in both the general population and in sports athletes [1]. Poor flexibility is a risk factor for cardiovascular disease [2]; poor trunk flexibility is associated with hypertension and arterial stiffness [3, 4]. Additionally, elite sports athletes with higher flexibility have a higher ROM than non-elite athletes [5, 6]. The flexibility parameters, such as ROM depend on the individual and are influenced by sex and age [7]. Joint flexibility is known to decrease with aging and be higher in females compared to males [7]. In addition, there are the genetic factors [8], since 38–61% of the traits associated with flexibility (based on assessments of "sit-and- reach") are heritable [8].

The *ACTN3* R577X polymorphism in the gene encoding α-actinin-3 (*ACTN3*), an actinin-binding protein involved in muscle structure, influences exercise performance [9]. In the *ACTN3* R577X polymorphism arginine (R) is converted to a stop codon (X) at position 1747 (exon 16) in *ACTN3* on chromosome 11. *ACTN3* deficiency is observed in the muscles of the XX carriers with *ACTN3* R577X polymorphism. *ACTN3* R577X polymorphism influences muscle strength [9] and power/sprint athletic status [10]. Because deficiency of α-actinin-3 alters muscle structure, the *ACTN3* R577X polymorphism is associated with muscle damage [11, 12] and muscle injury [13–15]. *ACTN3* R577X polymorphism, which regulates α-actinin-3 expression, influences not only muscle contractile properties such as muscle strength and power but also flexibility. *ACTN3* R577X polymorphism influences flexibility parameters such as muscle stiffness (using shear wave elastography), skinned fiber Young's modulus and hysteresis, and ROM [16–18]. The X allele or XX genotype carriers showed greater flexibility compared with those with

the RR genotype or R allele carriers. In addition, athletic status in artistic gymnasts and sport climbers, who require flexibility, is related to the frequency of the *ACTN3* R577X polymorphism [19, 20]. In artistic gymnasts, the *ACTN3* XX genotypes show higher athletic performance than the RR and RX genotypes [20], and the XX genotype was underrepresented in male gymnasts compared to controls [21]. A meta-analysis of three ethnic cohorts (Japanese, Polish, and Russian) showed that the frequency of the XX + RX genotypes in the *ACTN3* R577X polymorphism was significantly higher in climbers than that in the non-climbers [19]. Therefore, *ACTN3* R577X polymorphism influences sports athlete status through the influence of *ACTN3* polymorphism on flexibility.

The association between *ACTN3* R577X polymorphism and ROM is mostly studied in the context of flexibility parameters. However, there is also a report that the *ACTN3* R577X polymorphism has no effect on ROM [22]. The aim of this meta-analysis and systemic review was to investigate the association between the *ACTN3* R577X polymorphism and ROM and to determine the model (dominant, recessive and additive models) that is associated with ROM.

Materials and Methods

Data collection

All available studies published before April 14, 2022, were identified and collected from PubMed (https://pubmed.ncbi.nlm.nih.gov) using the following keywords and Boolean search operators : ("flexibility" OR "Joint Range of Motion" OR "Joint Flexibility" OR "Range of motion") AND ("ACTN3" OR "alpha-actinin 3").

Inclusion criteria

Studies that met the following criteria were included: (1) published in English, (2) human subject research, (3) ROM is measured, and (4) *ACTN3* R577X genotype has been analyzed. This review considered ROM measurement tests such as sit-and-reach, straight leg test, and chair sit-and-reach.

The search aimed to obtain papers that reported an association between *ACTN3* R577X polymorphism and ROM. In the first round of evaluation, the literature screen was based on the title and abstract. Papers that did not meet the inclusion criteria were excluded. In the second round, the full text of the selected papers was analyzed, and studies that lacked comparable quantitative data and measurements of physical performance were excluded. However, the reference lists of these excluded articles were inspected for relevant papers that were missed.

Data extraction and risk of bias assessment

From each selected study, the following data were extracted: (1) lead author names and year of publication, (2) subject characteristics, (3) ROM measurements, and (4) mean and standard deviation (SD) of the ROM measurements.

For risk of bias assessment, we used the Cochrane Risk of Bias tool [23], which considers selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias.

Statistics

All analyses were conducted using R (version 4.1.3) and its "meta" package. The additive genetic model was assessed using a meta-regression model. Dominant and recessive models were analyzed using a random effects model [24]. Heterogeneity across studies was evaluated using the mean of I^2 statistics. Egger's test and funnel plots were used to evaluate publication bias [25]. The relationship between flexibility, sex, and age was assessed using meta-regression in the sub-analysis. In the sub-analysis, we were unable to use the Juan Del Coso et al. 2019 data by sex and age, so we divided age into 20 s, over 40 s, and 28 – 65 years, and sex into man, woman, and man-woman.

Results

Risk of bias

▶ **Fig. 1** shows the risk of bias of the studies included in the present study. Blinding participants and personnel (preference bias) and blinding of outcome assessment (detection bias) were not mentioned by any study. In incomplete outcome data (attrition bias), only two studies described the reasons for excluding subjects, and in both cases subject selection was not arbitrary. All other sources of bias had low risk.

Systematic review

We identified 26 articles after applying the search filters (▶ **Fig. 2**). Seventeen articles were excluded in the first round, and two articles were excluded in the second round of screening. We believe that no papers were missed, based on the inspection of the reference lists. A total of 2908 participants from seven reports were included in the meta-analysis. The details of these reports are presented in ▶ **Table 1**. There were no studies that duplicates cohort of subjects. Some papers included multiple ROM measurements from multiple cohorts.

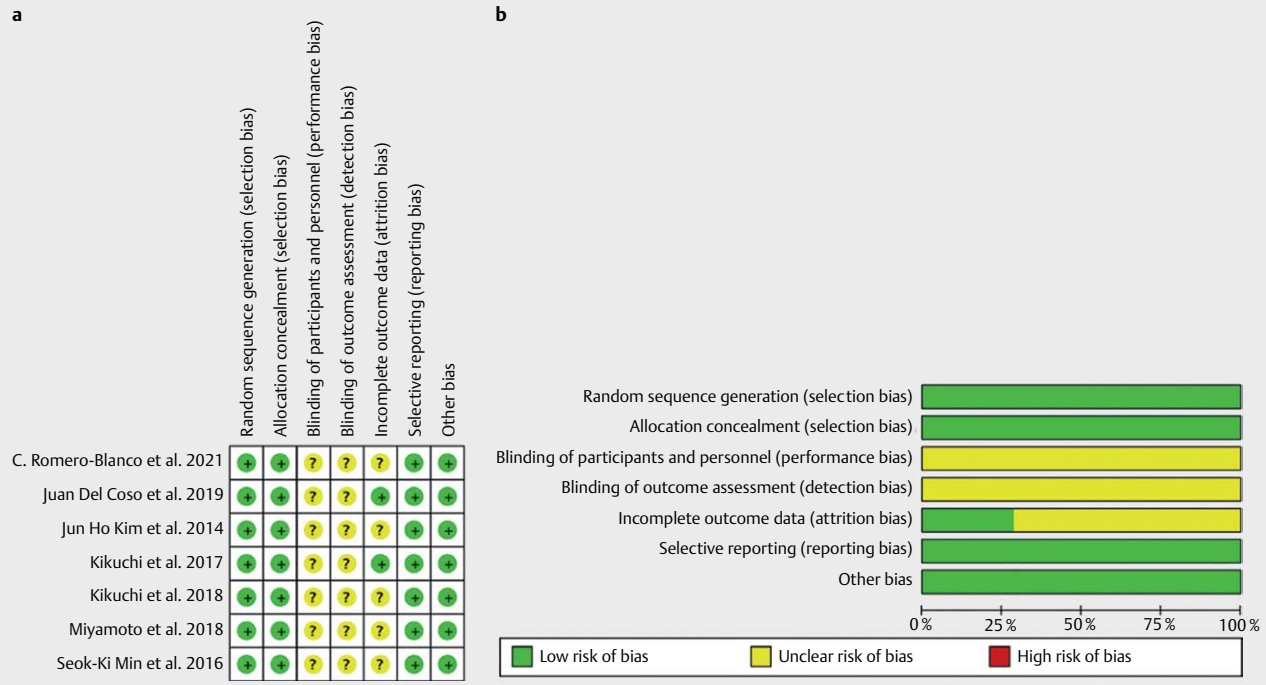
Meta-analysis

The associations between *ACTN3* R577X genotype and flexibility were not affected by publication bias in both dominant ($p = 0.939$) and recessive ($p = 0.980$) models. There was no significant association in the dominant model (standardized mean difference (SMD): 0.01, 95 % CI: –0.14, 0.15, $p = 0.941$, ▶ **Fig. 3a**). The recessive model showed a significant association between *ACTN3* R577X polymorphism and ROM, where the XX + RX genotypes had significantly higher ROM than the RR genotype (SMD: 0.15, 95 % CI: 0.006–0.23, $p < 0.001$, ▶ **Fig. 3b**). A sub-analysis of the recessive model indicated that age and sex did not influence the relationship (age: $p = 0.745$, sex: $p = 0.997$).

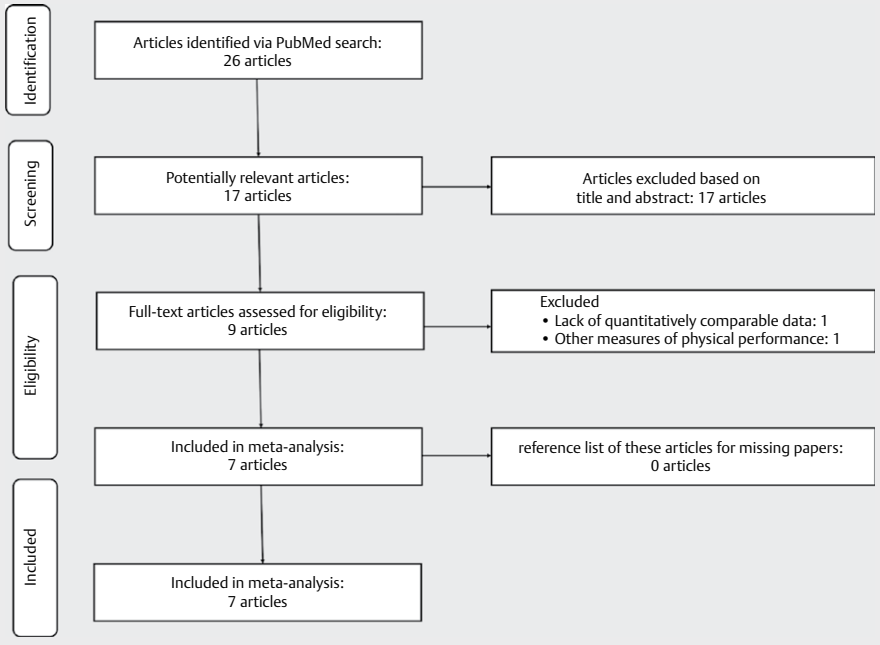
In addition, an additive relationship was observed; the flexibility was in the order XX, RX, and RR ($p = 0.029$, ▶ **Fig. 4**).

Discussion

We performed a systematic review and meta-analysis of the association between *ACTN3* R577X polymorphism and ROM in the dominant, recessive, and additive models. The ROM in the XX + RX genotype was significantly higher than that in the RR genotype (reces-



▶ **Fig. 1** Risk of bias summary (**a**) and risk of bias graph (**b**).



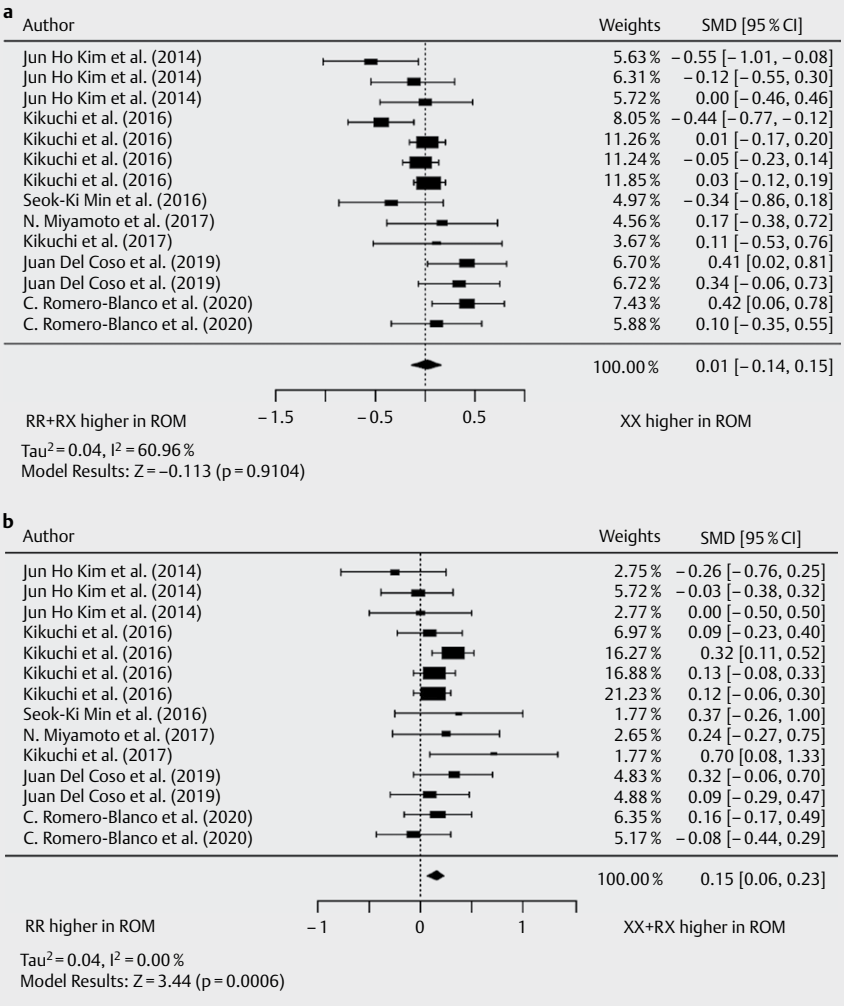
▶ **Fig. 2** Flowchart outlining the article-retrieval process and articles meeting criteria for the systematic review and meta-analysis.

sive model, $p < 0.001$), and it additively increased in the genotypes in the following order: XX > RX > RR (additive model, $p = 0.029$). However, no significant association was observed in the dominant model. These relationships were not influenced by sex or age.

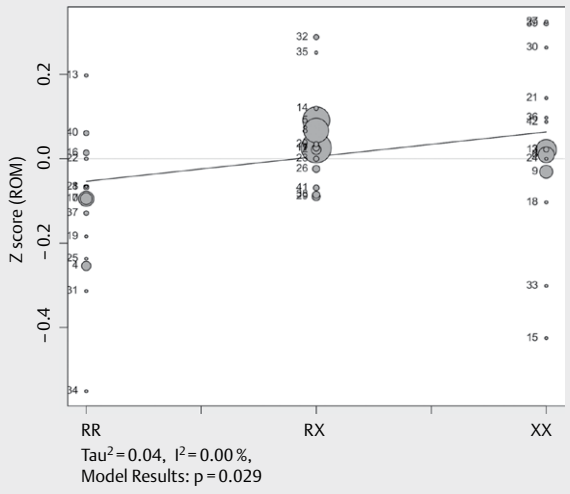
The *ACTN3* R577X genotype is a knockout variant, and *ACTN3* deficiency is observed in the individuals with XX genotype [26]. The *ACTN3* R577X polymorphism alters muscle contractile properties [27]. In addition, there was a negative correlation between

▶ **Table 1** Studies on the association between the *ACTN3* R577X polymorphism and ROM that were included in the meta-analysis.

No.	Author	Year	Sex	Cohort	Age	n	Phenotype	Reference
1	Jun Ho Kim et al.	2014	Women	Ballet dancers	20.9 ± 2.4	97	Sit-and-reach	[46]
2	Jun Ho Kim et al.		Women	Ordinary population	25.3 ± 4.4	151	Sit-and-reach	[46]
3	Jun Ho Kim et al.		Women	Ballet dancers	20.9 ± 2.4	97	Straight leg raise	[46]
4	Kikuchi et al.	2017	Men	Cohort 1	51.1 ± 13.6	208	Sit-and-reach	[18]
5	Kikuchi et al.		Women	Cohort 1	54.6 ± 11.8	568	Sit-and-reach	[18]
6	Kikuchi et al.		Men	Cohort 2	48.9 ± 15.7	529	Sit-and-reach	[18]
7	Kikuchi et al.		Women	Cohort 2	49.9 ± 14.6	728	Sit-and-reach	[18]
8	Seok-Ki Min et al.	2016	Women	–	67.38 ± 3.68	68	Chair sit-and-reach	[22]
9	Miyamoto et al.	2018	Men	–	21.2 ± 2.8	76	Straight leg raise	[16]
10	Kikuchi et al.	2018	Men	–	20.8 ± 3.8	52	Elbow joint angle	[47]
11	Juan Del Coso et al.	2019	Men and women	–	28–65	136	Ankle dorsiflexion	[48]
12	Juan Del Coso et al.		Men and women	–	28–65	136	Sit-and-reach angle	[48]
13	C. Romero-Blanco et al.	2021	Women	Cohort 1	69.7 ± 3.2	164	Chair sit-and-reach	[49]
14	C. Romero-Blanco et al.		Women	Cohort 2	78.5 ± 3	131	Chair sit-and-reach	[49]



▶ **Fig. 3** Forest plot of the **a**: Dominant (RR + RX vs. XX) model and B: Recessive (RR vs. XX + RX) model. ROM, range of motion; SMD, standardized mean difference



▶ **Fig. 4** Bubble plot of the additive model.

ROM and passive muscle stiffness, as observed using share-wave elastography [28]. Passive muscle stiffness was lower in the XX genotype than that in the RR + RX genotype [16]. In contrast, higher passive muscle stiffness contributes to a rapid force, such as the rate of torque development [29]. The RR genotype, with a high passive muscle stiffness, showed rapid force, including squat and countermovement jumps, compared to the XX genotype [30]. The *ACTN3* R577X polymorphism influences rapid force production and ROM through changes in the muscle properties.

There is an association between the *ACTN3* R577X genotype and ROM. Broos et al. examined Young's modulus and hysteresis in human type IIa/IIx fibers and suggested that these passive tensions significantly increased with each additional R allele [17]. The results from the meta-analysis are consistent with those of Broos et al. [17]. The concentration of theα-actinin-2 (ACTN2) protein in KO mice was higher than that in wild-type mice, suggesting that in its absence, the *ACTN3* in the muscle is replaced with another protein from the same family [31]. A higher expression of ACTN2 could lead to lower passive tension because ACTN2 has a higher binding affinity with titin. Titin is a major determinant of the passive stiffness of the sarcomere, especially in type I fibers. Low concentrations of titin is correlated with a low Young's modulus (Tourse et al., 2002); ACTN2 changes the concentration and organization of titin in the muscle.

In this meta-analysis and systematic review, a higher ROM was observed in the XX + RX genotype than in the RR genotype (recessive model); the ROM increased additively in the genotypes in the following order: XX > RX > XX (additive model). Garton et al. reviewed the effect of *ACTN3* R577X polymorphism on human muscle performance [9]. In healthy adults, strength/power performance was higher in the RR genotype than that in the XX + RX genotypes (dominant model) and increased additively in the following order: RR > RX > XX (additive model). Therefore, the heterozygote RX could confer both muscle strength and power characteristics, and flexibility. ACTN2 expression is additively increased in the order RR > RX > XX in *ACTN3* KO mice [32]. Therefore, the differential expression of ACTN2, regulated by the *ACTN3* R577X polymorphism, could play a key role in the additive association.

Age and sex influence flexibility [33]; however, in this meta-analysis, age and sex did not have an impact in the sub-analysis. Therefore, age and sex might not affect the association between the *ACTN3* R577X polymorphism and flexibility.

The frequency of the *ACTN3* X allele is lower than 10 %, 45 %, and 50 % in the African, European, and Asian populations, respectively, and more than 70 % in the American population [34, 35]. The X allele of the *ACTN3* R577X polymorphism is considered a polymorphic subject of positive selection during human migration from the African to the Eurasian climate, which is colder and less species-rich [36]. The XX genotype has a lower resting systolic and diastolic blood pressure than the RR genotype [37]. The change in the *ACTN3* expression levels in the arteries could explain the difference in the resting systolic blood pressure. *ACTN3* deficiency inhibits the progression of dystrophic pathology [38]. In addition, centenarian individuals show a higher frequency of the X allele than professional road cyclists with an extreme muscle endurance phenotype and with the highest frequency of X allele in non-athletic populations [39]. In this study, *ACTN3* deficiency influences flexibility. Flexibility traits including ROM, is an important physical fitness characteristic [1], and is associated with risk factors for cardiovascular diseases [2]. Therefore, the effect of the *ACTN3* R577X polymorphism on ROM may indirectly construe a positive influence on health. In addition, *ACTN3* deficiency could provide an advantage to athletes who need flexibility.

Several studies have examined the association between other gene polymorphisms and flexibility [40, 41]. For instance, the *COL1A1* (rs1107946) and *COL5A1* (rs12722) polymorphisms are associated with ROM [40, 41]. Gene polymorphisms are associated with genu recurvatum and general joint laxity (sports, exercise, and nutritional genomics). However, no polymorphism is associated with ROM, apart from the *ACTN3* R577X polymorphism. Therefore, the *ACTN3* R577X is a unique polymorphism that influences flexibility.

Generally, low ROM is known to increase the risk of muscle injury [42–44]. However, the X allele of *ACTN3* R577X polymorphism has a higher ROM than the RR genotype and a higher risk of muscle injury [13–15]. A previous study suggested that the X allele had higher muscle damage such as creatine kinase activity and muscle soreness compared to the RR genotype [45]. The relationship between the high flexibility of X allele and muscle injury is unclear and should be examined in future study.

This study has a few limitations. The number of reports included appears fewer because we could not find more papers that met the inclusion criteria. Flexibility parameters are not limited to ROM. Therefore, it is necessary to examine the exhaustive effect of the *ACTN3* R577X polymorphism on flexibility in future studies. Several factors affect ROM apart from muscle properties. The results of the sit-and-reach test are influenced not only by muscle stiffness but also by tendon and ligament stiffness. Therefore, the effects of the *ACTN3* R577X polymorphism on flexibility should be investigated using multiple methods and by considering interaction effects, including other genetic factors.

In conclusion, the ROM in XX + RX genotypes was significantly higher than that in the RR genotype. ROM was additively higher in the genotypes in the following order, XX > RX > RR.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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