Hattori *et al.*
Journal of Physiological Anthropology (2026) 45:24
https://doi.org/10.1186/s40101-026-00439-5

Journal of
Physiological Anthropology

REVIEW

Open Access

Association between the *ACTN3* R577X polymorphism and skeletal muscle mass: a systematic review and meta-analysis

Sakura Hattori[1*], Mika Kamiya-Saito[2], Naoki Kikuchi[1,2] and Koichi Nakazato[1,2]

Abstract

Background The *ACTN3* R577X polymorphism is one of the genetic factors influencing skeletal muscle mass. Although several studies have reported that the X allele of the *ACTN3* R577X polymorphism is associated with reduced muscle mass, others have found no significant relationship between genotype and muscle mass. These inconsistencies may be explained by differences in background characteristics of the study populations, such as sex, age, ethnicity, and measurement site. This systematic review and meta-analysis aimed to clarify the association between the *ACTN3* R577X polymorphism and skeletal muscle mass. In addition, we investigated whether the effect of the *ACTN3* gene is modified by population background.

Main body A total of 34 cohorts (9,496 participants) derived from 24 studies were included in the meta-analysis. In the overall analysis under the dominant model for the X allele (RR vs. RX + XX), the *ACTN3* genotype showed a significant effect on skeletal muscle mass (SMD [95% CI] = − 0.08 [− 0.15 to − 0.02], $p = 0.014$), with the RX + XX group exhibiting lower skeletal muscle mass compared with the RR group. In contrast, the recessive model (RR + RX vs. XX) did not yield a statistically significant effect (SMD [95% CI] = − 0.02 [− 0.12 to 0.07], $p = 0.616$). Under the additive model, a trend toward an effect was observed (per-allele; β [95% CI] = − 0.05 [− 0.10 to 0.01], $p = 0.078$). Moderate heterogeneity was observed across all models (dominant: $I^2 = 38.8\%$; recessive: $I^2 = 55.8\%$; additive: $I^2 = 52.5\%$). No significant subgroup effects were observed for sex, age, or ethnicity. Meta-regression for measurement site indicated that the association became more pronounced as lower-limb specificity increased, although residual heterogeneity remained.

Conclusion The *ACTN3* R577X polymorphism showed a small association with skeletal muscle mass under the X-allele dominant model, suggesting that this association may be detectable even in heterozygous individuals. Although measurement site may modulate this association, none of the examined factors substantially explained the observed heterogeneity when considered individually. The remaining variability may reflect combinations of background characteristics that were not fully captured by single-factor analyses. Further studies accounting for background characteristics are warranted to clarify the genetic contribution of *ACTN3* R577X to skeletal muscle mass.

Keywords ACTN3, α-actinin-3, ACTN3 R577X polymorphism, Skeletal muscle mass, Sarcopenia

*Correspondence:
Sakura Hattori
25sda11@nittai.ac.jp
[1] Graduate School of Health and Sport Science, Nippon Sport Science University, Tokyo, Japan
[2] Research Institute for Sport Science, Nippon Sport Science University, Tokyo, Japan

© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Introduction

Sarcopenia is recognized not merely as a decline in musculoskeletal function but as a risk factor for various diseases [1]. Skeletal muscle serves multiple critical physiological roles beyond mechanical support, functioning as a glucose metabolic tissue [1, 2], an endocrine organ [3], an energy reservoir [4, 5], and a site for drug metabolism [6–8]. Therefore, maintaining adequate skeletal muscle mass is essential for preventing age-related sarcopenia and frailty, reducing the risk of lifestyle-related diseases, and improving clinical outcomes across diverse medical conditions.

The importance of genetic determinants in individual differences in skeletal muscle mass and sarcopenia has been increasingly recognized in recent years. Twin and family studies have reported that heritability estimates for muscle mass–related traits, including lean body mass, limb circumference, and cross-sectional area, range from approximately 56% to over 80%, depending on adjustment factors [9–13]. Elucidating the mechanisms underlying this diversity in muscle mass may enable personalized risk management and the prevention of sarcopenia. Despite the identification of numerous associated genes [14], the full landscape of genetic factors determining skeletal muscle mass remains unclear.

The *ACTN3* rs1815739 polymorphism is one of the genetic factors suggested to be associated with skeletal muscle mass. This variant leads to the replacement of an arginine residue with a premature stop codon at position 577 (R577X), a nonsense allele. *ACTN3* knockout (KO) mice, which model the R577X, have demonstrated that deficiency of α-actinin-3, encoded by the *ACTN3* gene, reduces skeletal muscle mass [15–18]. Although these animal studies consistently support the association between *ACTN3* genotype and muscle mass, findings in humans remain inconsistent. Zempo et al. (2010) reported that RR + RX genotype exhibited greater muscle mass than the XX genotype [19], whereas a large cohort study by Delmonico et al. (2008) found no significant genotype-related differences [20].

These inconsistencies may be attributable not only to limitations in statistical power due to small sample sizes, but also to differences in population characteristics, such as age [21, 22] and sex [21, 23, 24], and in assessment methods, including the measurement site from which skeletal muscle mass was evaluated [25, 26]. In addition, given that the *ACTN3* polymorphism has been suggested to have undergone evolutionary selection pressures [15, 27, 28], it is plausible that differences in genetic background across populations may further modify the phenotypic effects of this variant. Thus, to elucidate the physiological significance of the *ACTN3* polymorphism, it is necessary to adopt a multifaceted perspective that considers not only the factors previously reported in the literature but also population-specific genetic contexts that may influence its effects.

Accordingly, the present study aimed to systematically evaluate the association between the *ACTN3* R577X polymorphism and skeletal muscle mass and to gain insights into factors that may modulate this association by conducting a meta-analysis along with subgroup analyses based on potential effect modifiers.

Method

Eligibility criteria

Only studies that investigated the association between the *ACTN3* R577X polymorphism and skeletal muscle mass were considered eligible for inclusion. Specifically, studies were included if they (1) examined the association between the *ACTN3* R577X polymorphism and skeletal muscle mass; (2) enrolled human participants, with no restrictions on age, sex, physical activity level, or athletic status; (3) reported quantitative measures of skeletal muscle mass, such as lean body mass (LBM), fat-free mass (FFM), muscle cross-sectional area (CSA), or muscle volume; and (4) were published as full-text articles in the English language.

Studies were excluded if they (1) were review articles, meta-analyses, animal studies, or in vitro experiments; (2) did not provide separate data for the *ACTN3* RX genotype in addition to the RR and XX genotypes; (3) lacked sufficient statistical data to calculate effect sizes (i.e., mean and standard deviation of skeletal muscle mass for each *ACTN3* R577X genotype); or (4) contained participant data that overlapped with a previously included publication.

Search strategy

The PubMed, Web of Science, and SPORTDiscus databases were searched up to November 2025 using the following search string: (ACTN3 OR actinin3 OR "alpha actinin3") AND ("muscle mass" OR "lean body mass" OR "muscle volume" OR "cross sectional area" OR "Muscular Atrophy" OR "Sarcopenia").

Study records

All search results were exported to Rayyan [29] and Microsoft Excel (Microsoft Corp.) for recordkeeping and data management. The Excel spreadsheets were used to document the search records and organize the extracted data. Full-text articles and associated datasets were stored in a shared Dropbox folder, which was accessible to all review authors.

Two authors independently screened the titles and abstracts of all retrieved records to identify potentially eligible studies. The full texts of the remaining articles

were subsequently assessed for eligibility. Any disagreements between reviewers were resolved through discussion. In addition, further relevant studies were identified by screening the reference lists of the included articles. Reasons for study exclusion at the full-text stage were systematically documented.

Data were independently extracted by two authors using a standardized extraction form. The following information was collected from each study: PubMed ID, article title, authors, journal name, year of publication, skeletal muscle mass data (mean, standard deviation [SD] or standard error [SE], and sample size for each genotype), participant characteristics (sex, age, country, height, weight), phenotype information, and methodological details. For studies involving training interventions, skeletal muscle mass data at baseline before the intervention were extracted. When necessary, the corresponding study authors were contacted to obtain summary statistics required for the meta-analysis.

Quality assessment

The methodological quality and risk of bias of the included studies were assessed using the Risk of Bias Assessment Tool for Non-randomized Studies, version 2 (RoBANS-2) [30], which is specifically designed to evaluate cross-sectional studies. Each study included in the meta-analysis was independently assessed for risk of bias by two reviewers. The assessment was performed separately for each participant group analyzed in the meta-analysis, and any disagreements were resolved through discussion. An overall risk-of-bias judgment for each study was determined according to the following predefined rules: a study was judged to have a high risk of bias if at least one domain was rated as High; a low risk of bias if all domains were rated as Low or if only one domain was rated as unclear; and an unclear risk of bias in all other cases.

Potential publication bias was evaluated by visually inspecting funnel plots and statistically tested using Egger's regression test [31].

Statistical analysis

Genotype effects were evaluated under three commonly used genetic models: dominant, recessive, and additive for the X allele. In the dominant model (RR vs RX + XX) and the recessive model (RR + RX vs XX), genotype groups were first collapsed according to the assumed inheritance pattern, and the standardized mean difference (SMD) was then calculated based on the resulting two-group comparison. Hedges' g was used as the SMD and was calculated from the mean, standard deviation, and sample size of each group to account for potential small-sample bias in individual studies [30]. In the additive model, genotypes were coded as 0 (RR), 1 (RX), and 2 (XX), and the per-allele effect size was calculated as the regression coefficient (β). All effect sizes were oriented so that more negative values indicated lower skeletal muscle mass in association with the X allele.

A random-effects model was used to synthesize the data, as heterogeneity among studies was anticipated. The Knapp-Hartung adjustment was applied to calculate the 95% CI for the pooled effect size, as this method provides a more robust estimate in the presence of heterogeneity [32]. Statistical heterogeneity was evaluated with Cochran's Q test and quantified using the I^2 statistic. Following the recommendations of Higgins et al. (2002), I^2 values of 25%, 50%, and 75% were interpreted as representing low, moderate, and high levels of heterogeneity, respectively [33].

Furthermore, to assess the robustness of the pooled results, a leave-one-out sensitivity analysis was performed. This involved iteratively removing one study at a time and recalculating the overall effect size to ensure that the results were not unduly influenced by any single cohort.

To explore potential sources of heterogeneity, we conducted subgroup analyses based on pre-specified study characteristics: sex, age, ethnicity, and measurement site. The age variable was dichotomized into two categories, defined as young (< 60 years old) and old (≥ 60 years old). The ethnicity was determined for each study based on participant information and the country where the experiment was conducted. The statistical significance of differences between subgroups was assessed using Cochran's Q test, and the degree of heterogeneity was quantified using the I^2 statistic [34]. For each subgroup analysis, datasets with missing data for the subgroup-defining variables were excluded on an analysis-specific basis.

To examine whether the effect size under the additive model varied according to measurement site, measurement-site categories were coded as an ordinal moderator reflecting increasing lower-limb specificity. Whole-body, four-limb, and lower-limb categories were assigned values of 0, 1, and 2, respectively. A meta-regression analysis was then performed with this ordinal variable entered as a continuous moderator. The model was fitted using restricted maximum likelihood estimation, and statistical inference for the moderator was based on the Knapp–Hartung adjustment. The proportion of heterogeneity explained by the moderator was expressed as R^2_*.

All analyses were performed using R (version 4.5.1) with the meta package (version 8.2.0) and metafor package (version 4.8.0). A two-sided p value < 0.05 was considered statistically significant for all analyses.

Result

Study selection

The study selection process is summarized in Fig. 1. Our initial database search yielded 187 potential articles. After removing 57 duplicates, 130 articles were screened. After excluding 81 records based on title and abstract review, we assessed 49 articles at the full-text level. In addition to the 19 studies identified from the primary search, five more were included through a reference search. Ultimately, 24 studies satisfied the eligibility criteria, from which 34 independent datasets were extracted and included in the meta-analysis.

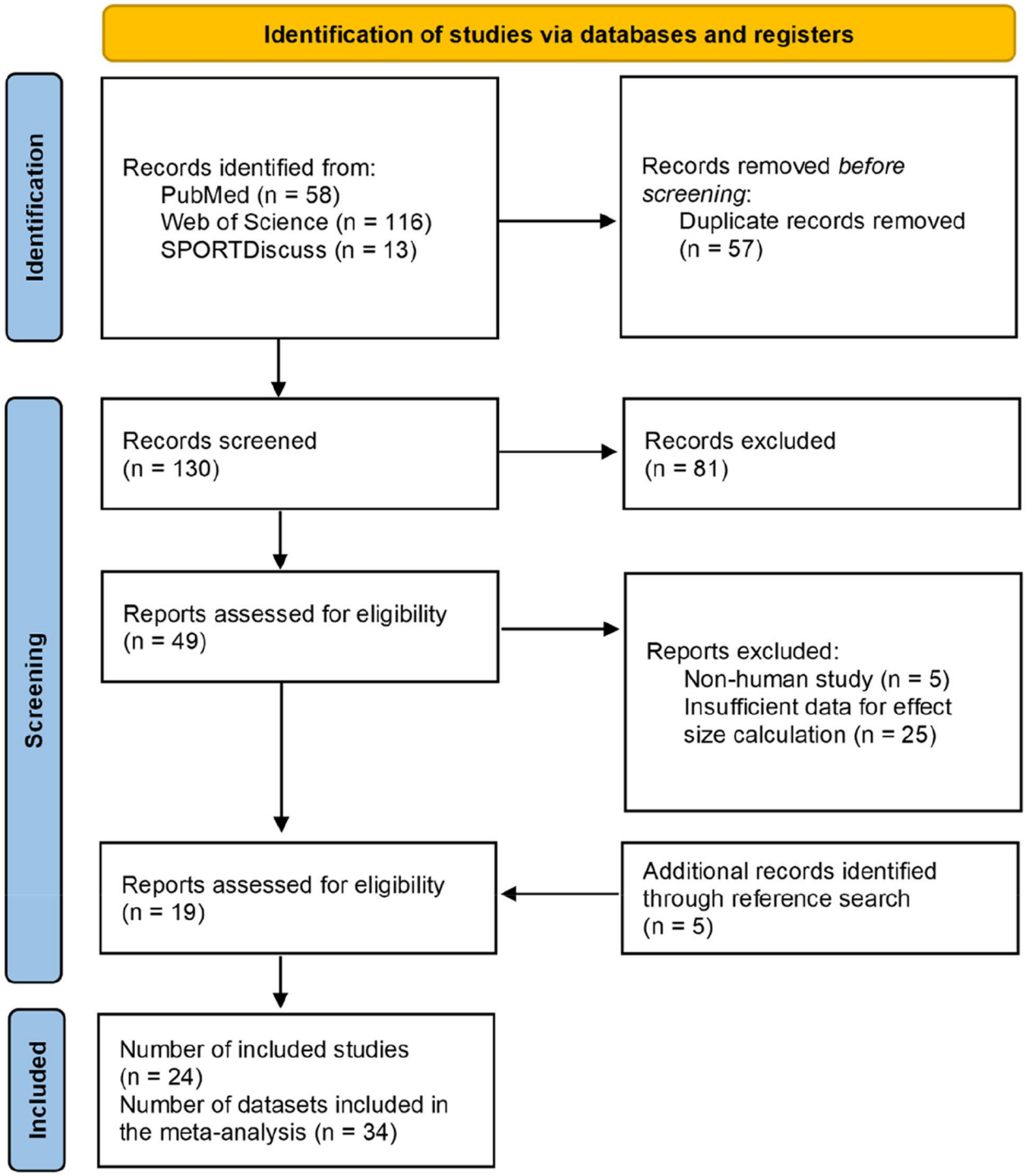


Fig. 1 PRISMA flow chart of the study selection procedure PRISMA flow diagram (adapted from the PRISMA 2020 template). Original from Page MJ et al. (2021) [35], licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/)

Study characteristics

A total of 24 studies were included, with sample sizes ranging from 32 to 1152 participants per cohort. The cohorts comprised both young (< 60 years) and old (≧ 60 years), and included male, female, or both sexes. Studies were conducted across East Asia, Europe, and admixed American groups. Outcomes included muscle volume, cross-sectional area, and fat-free mass, assessed using dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), Bioelectrical Impedance Analysis (BIA), or skinfold methods, with measurements reported for either appendicular or whole-body compartments. The detailed characteristics of the included studies are presented in Table 1.

Publication bias and risk-of-bias assessment

The results of the risk-of-bias assessment are summarized as a traffic-light plot in Additional file 1. Overall, 13 analyses were judged to have a high risk of bias, 14 were judged as low risk, and 7 were unclear. The primary domains contributing to a High risk of bias were Confounders (D3), followed by Comparability of the target group (D1), Blinding of assessors (D5), Outcome assessment (D6), and Incomplete outcome data (D7). The risk

Table 1 Characteristics of studies were included in meta-analysis

Study	Sex	*N*	Age	Age group	Country	Ethnicity	Outcome	Unit	Body region
Boshnjaku et al. 2021 [36]	B	282	67.6	Old	Kosovan	European	FFM (BIA)	kg	Whole
Cho et al. 2017 [37]	B	332	≧ 65	Old	Korea	East Asian	MV (DEXA)	kg/m^2	Four limbs
Kiuchi et al. 2021 [38]	B	64	74.5	Old	Japan	East Asian	MV (MRI)	cm^3	Lower limbs
Zempo et al. 2010 [26]	F	109	64.1	Old	Japan	East Asian	CSA (MRI)	cm^2	Lower limbs
Broos et al. 2015 [39]	M	266	20.9	Young	Belgium	European	CSA (Skinfold)	cm^2	Lower limbs
Lima et al. 2011 [40]	F	234	66.7	Old	Brazil	Admixed American	FFM (BIA)	kg	Whole
Min et al. 2016 [41]	F	68	67.4	Old	Korea	East Asian	MV (DEXA)	kg	Whole
Zempo et al. 2011a [22]	F	82	50.6	Young	Japan	East Asian	CSA (MRI)	cm^2	Lower limbs
Zempo et al. 2011b [22]	F	80	66.8	Old	Japan	East Asian	CSA (MRI)	cm^2	Lower limbs
Erskine et al. 2014 [42]	M	51	20.3	Young	(Caucacian)	European	MV (MRI)	cm^3	Lower limbs
Urzi et al. 2021a [43]	M	67	65–78	Old	Slovenia	European	FFM (BIA)	kg/m^2	Whole
Urzi et al. 2021b [43]	F	123	65–78	Old	Slovenia	European	FFM (BIA)	kg/m^2	Whole
Delmonico et al. 2008a [20]	M	726	73.9	Old	America (White)	European	MV (DEXA)	kg	Lower limbs
Delmonico et al. 2008b [20]	F	641	73.5	Old	America (White)	European	MV (DEXA)	kg	Lower limbs
Delmonico et al. 2008c [20]	M	1152	73.7	Old	America (White)	European	MV (DEXA)	kg	Lower limbs
Clarkson et al. 2005a [44]	M	247	24.9	Young	N/A	N/A	CSA (MRI)	cm^2	Upper limbs
Clarkson et al. 2005b [44]	F	355	24.3	Young	N/A	N/A	CSA (MRI)	cm^2	Upper limbs
Vincent et al. 2007 [45]	M	90	21.7	Young	Belgium	European	FFM (BIA)	kg	Whole
Walsh et al. 2008a [46]	M	416	22–90	N/A	N/A	N/A	MV (DEXA)	kg	Whole
Walsh et al. 2008b [46]	F	394	22–90	N/A	N/A	N/A	MV (DEXA)	kg	Whole
Norman et al. 2009a [47]	M	61	25.3	Young	Sweden	European	FFM (Skinfold)	kg	Whole
Norman et al. 2009b [47]	F	59	24	Young	Sweden	European	FFM (Skinfold)	kg	Whole
McCauley et al. 2010 [48]	M	100	65	Old	United Kingdom	European	MV (DEXA)	kg	Whole
Hanson et al. 2010 [49]	B	57	22	Young	N/A	N/A	FFM (Skinfold)	kg	Whole
Abudurezake et al., 2025a [50]	M	603	72.9	Old	Japan	East Asian	FFM (BIA)	kg	Four limbs
Abudurezake et al., 2025b [50]	F	881	73	Old	Japan	East Asian	FFM (BIA)	kg	Four limbs
Iwasaka et al., 2024a [51]	M	404	61.3	Old	Japan	East Asian	FFM (BIA)	kg/m^2	Whole
Iwasaka et al., 2024b [51]	F	619	60.8	Old	Japan	East Asian	FFM (BIA)	kg/m^2	Whole
Silva et al., 2024a [52]	B	32	69.5	Old	Brazil	Admixed American	N/A	kg/m^2	Whole
Silva et al., 2024b [52]	B	39	63	Old	Brazil	Admixed American	N/A	kg/m^2	Whole
Shin et al., 2024 [53]	N/A	81	29.3	Young	Korea	East Asian	FFM (BIA)	kg	Whole
Taniguchi et al., 2022 [54]	B	295	73.2	Old	Japan	East Asian	FFM (BIA)	kg/m^2	Four limbs
Güereca-Arvizuo J et al., 2022 [55]	M	35	18–35	Young	Mexico	Admixed American	FFM (BIA)	kg	Whole
Shang et al., 2012 [56]	M	452	21.0	Young	China	East Asian	FFM (BIA)	kg	Whole

Age groups were defined as young (< 60 years) and older (≥ 60 years). Parentheses (e.g., "Caucasian") denote studies in which the country was not reported and only race was provided. Parentheses in the Outcome column indicate the measurement method. *Abbreviations*: *B* both sex, *F* female, *M* male, *FFM* free-fat mass, *MV* muscle volume, *CSA* cross-sectional area, *BIA* bioelectrical impedance analysis, *DEXA* dual-energy X-ray absorptiometry, *MRI* magnetic resonance imaging

of bias summary was presented with consideration of study weights from the random-effects model used in the meta-analysis (Additional file 1). Using this weighting approach, studies with a high risk of bias accounted for approximately 25% of the evidence across the dominant, recessive, and additive models.

Funnel plots for all genotype models are shown in Additional file 2. Egger's test indicated no significant publication bias in any of the genotype models (dominant: $p=0.174$, recessive: $p=0.910$, additive: $p=0.290$).

Overall effect of the genotype

Under the X allele dominant model, a statistically significant association between the *ACTN3* genotype and skeletal muscle mass was observed, with the combined RX + XX genotype group exhibiting lower skeletal muscle mass compared with the RR genotype group (Fig. 2; SMD = − 0.08 [95% CI − 0.15 to − 0.02], $p=0.014$). In contrast, the pooled analysis under the recessive model did not show a significant association between *ACTN3* genotype and skeletal muscle mass (Fig. 3; SMD = − 0.02 [95% CI − 0.12 to 0.06], $p=0.616$). Under the additive model, there was a trend toward an association (Fig. 4; β = − 0.05 [95% CI − 0.10 to 0.00], $p=0.078$). All model demonstrated moderate heterogeneity (dominant: I^2 38.8%; Cochran's Q $p=0.014$, recessive: I^2 55.8%; Cochran's Q $p<0.001$, additive: I^2 52.5%; Cochran's Q $p<0.001$). Leave-one-out sensitivity analyses indicated that the results were robust, with detailed results presented in Additional file 3.

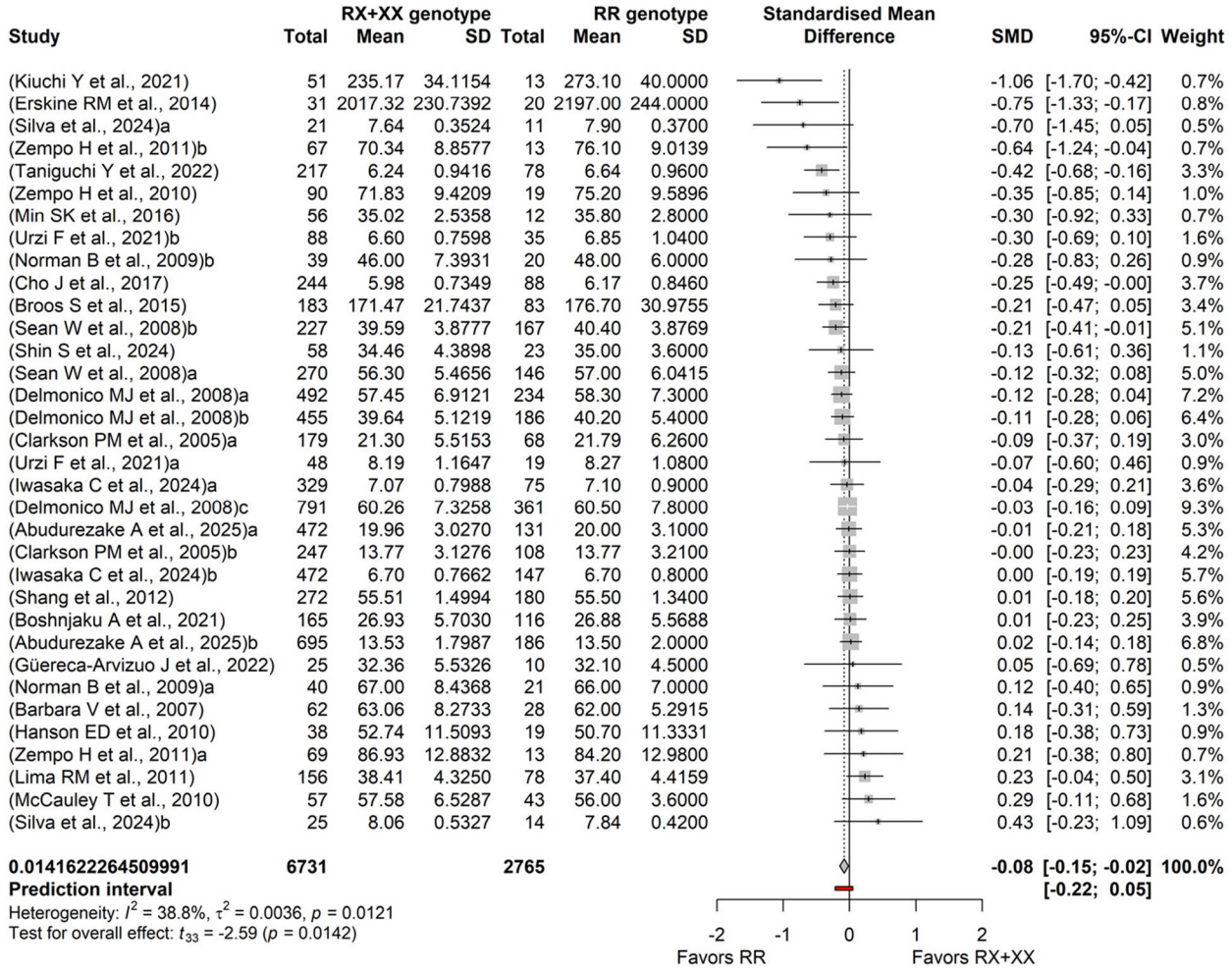


Fig. 2 Forest plot comparing skeletal muscle mass between the RR and RX + XX (dominant model) Each square represents the standardized mean difference (SMD) for an individual study, with the horizontal lines indicating 95% confidence intervals (CI). The size of each square is proportional to the study weight under the random-effects model. The diamond at the bottom represents the overall pooled estimate and its 95% CI. Heterogeneity was assessed using the I^2 statistic, with an I^2 value of 38.8%, indicating moderate heterogeneity. The p-value for heterogeneity was calculated using Cochran's Q test ($p=0.0121$). Positive SMD values favor the RX + XX genotype, whereas negative values favor the RR genotype

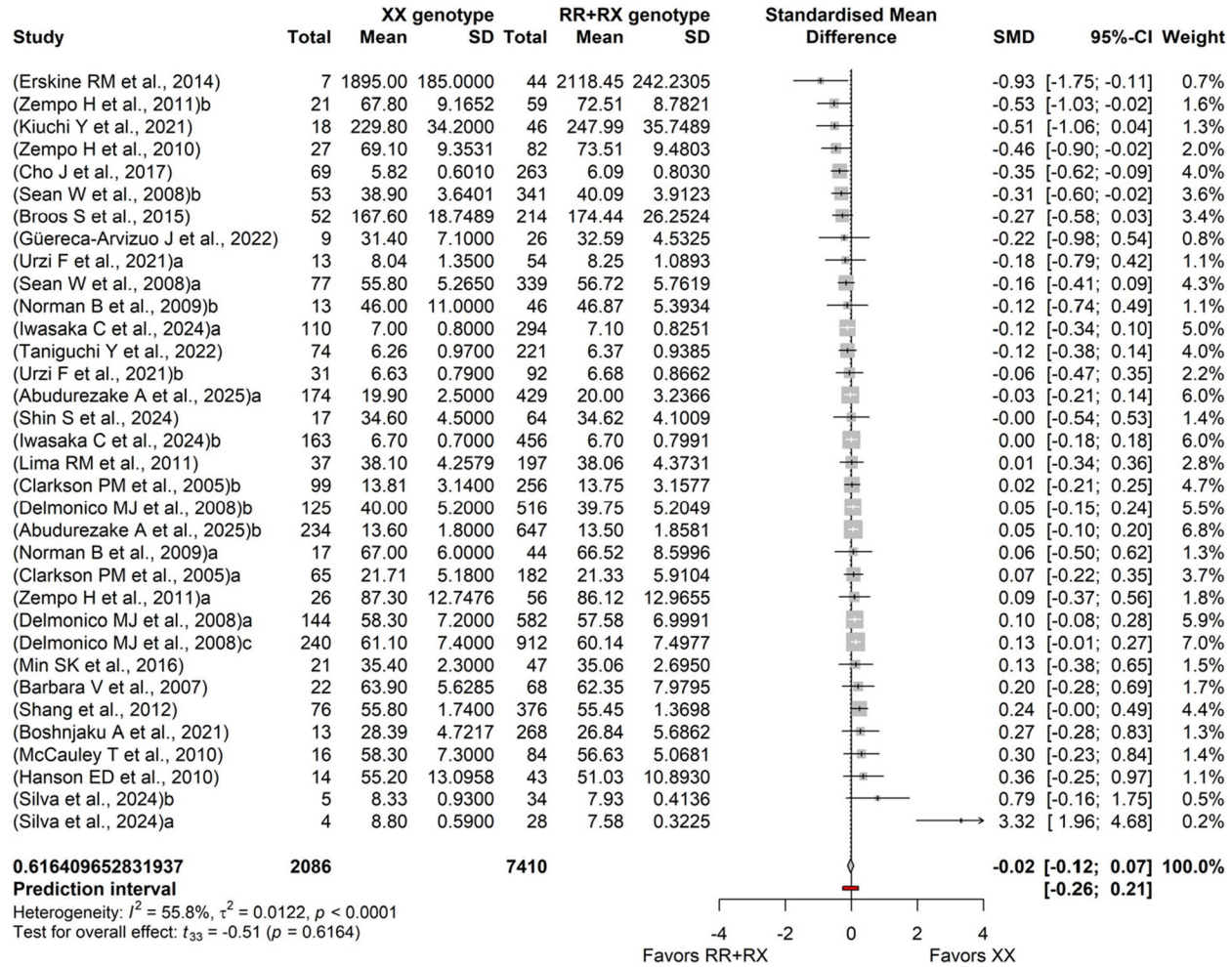


Fig. 3 Forest plot comparing skeletal muscle mass between the RR + RX vs XX (recessive model). Each square represents the standardized mean difference (SMD) for an individual study, with the horizontal lines indicating 95% confidence intervals (CI). The size of each square is proportional to the study weight under the random-effects model. The diamond at the bottom represents the overall pooled estimate and its 95% CI. Heterogeneity was assessed using the I^2 statistic, with an I^2 value of 55.8%, indicating moderate heterogeneity. The *p*-value for heterogeneity was calculated using Cochran's *Q* test ($p < 0.0001$). Positive SMD values favor the XX genotype, whereas negative values favor the RR + RX genotype

Subgroup analysis

We conducted subgroup analyses to explore potential sources of heterogeneity according to sex, age group, ethnicity, and measurement site across all three genetic models. The results of the subgroup analysis are presented in Table 2. In the additive model, there was a trend toward differences in effect size according to measurement site (between-subgroup $I^2 = 60.18\%$, $p = 0.08$; whole body: β = − 0.01 [95% CI − 0.07 to 0.06]; four limbs: β = − 0.09 [95% CI − 0.30 to 0.11]; lower limbs: β = − 0.19 [95% CI − 0.39 to 0.01]).

Because the measurement-site categories could be interpreted as reflecting increasing lower-limb specificity, whole body, four limbs, and lower limbs were coded as an ordinal variable with values of 0, 1, and 2, respectively. To examine whether differences in effect size across measurement sites followed an ordinal trend, we performed a meta-regression analysis using this ordinal variable. The meta-regression analysis showed a negative association between the ordinal measurement-site variable and effect size (Fig. 5; β = − 0.072 [95% CI − 0.140 to − 0.004], $p = 0.039$), indicating that the X allele was more strongly associated with lower muscle mass as the measurement site became more specific to the lower limbs. However, this linear trend did not explain the overall heterogeneity (R^2_*, amount of heterogeneity accounted for = 0.00%). Therefore, we visually explored whether the trend across measurement sites coincided with other study-level

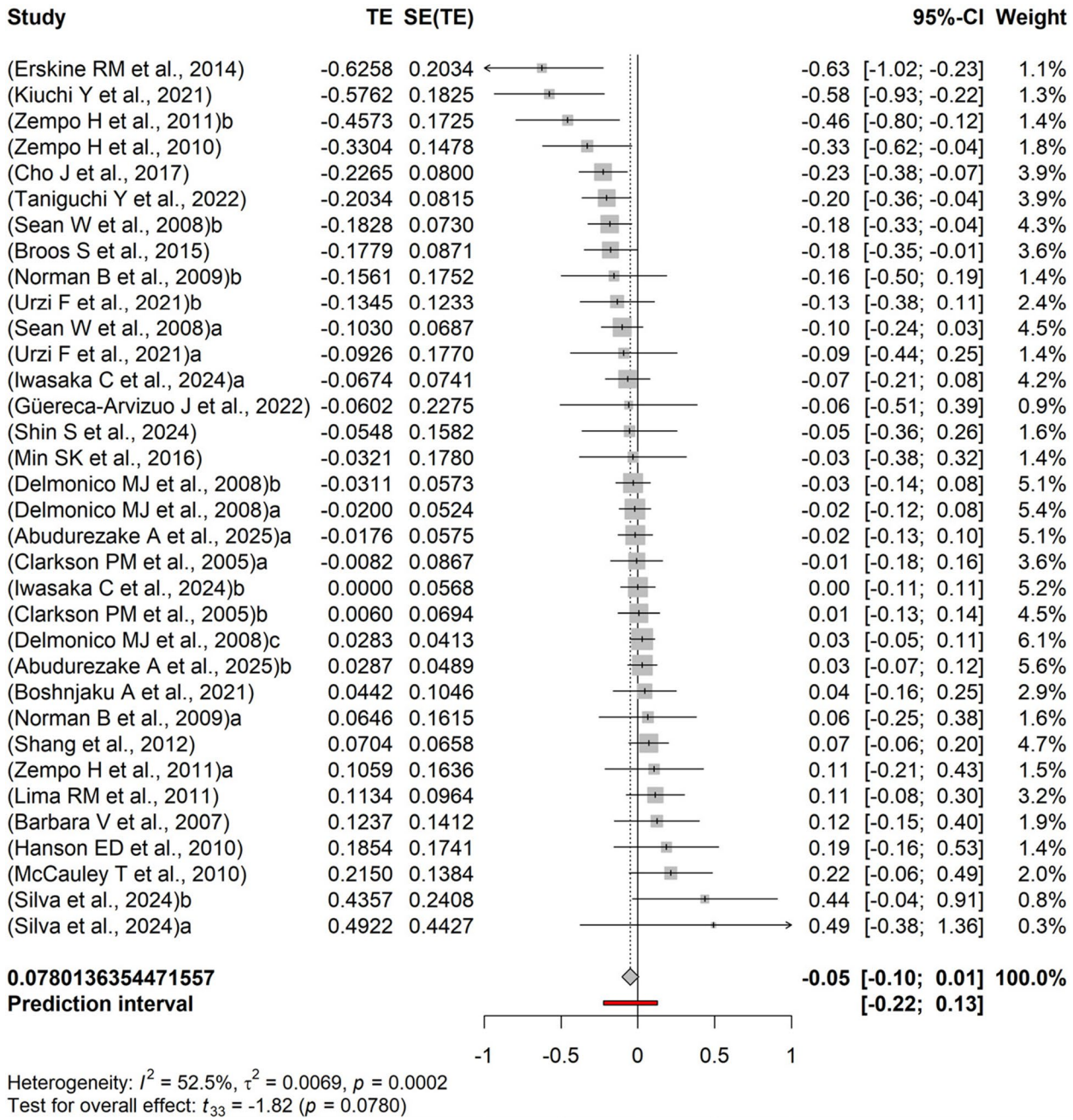


Fig. 4 Forest plot comparing skeletal muscle mass across *ACTN3* genotypes (additive model). Each square represents the regression coefficient (β) for an individual study, with the horizontal lines indicating 95% confidence intervals (CIs). The size of each square is proportional to the study weight under the random-effects model. The diamond at the bottom represents the overall pooled estimate and its 95% CI. Heterogeneity was assessed using the I^2 statistic, with an I^2 value of 52.5%, indicating moderate to substantial heterogeneity. The *p*-value for heterogeneity was calculated using Cochran's *Q* test ($p = 0.0002$). Negative β values indicate a greater muscle mass associated with the R allele

characteristics, such as ethnicity and age group. Visual inspection of the plot suggested that some datasets involving EAS populations, older participants, and lower-limb measurements showed more negative effect sizes, as indicated by the orange circles (Fig. 5).

Discussion

This systematic review and meta-analysis investigated the association between the *ACTN3* R577X polymorphism and skeletal muscle mass. The overall effect on the dominant model was statistically significant, with the

Table 2 Subgroup analysis results across sex, age, ethnicity, and body region groups

Model	Subgroup	*k*	n.e	n.c	ES (95% CI)	I^2	*p*-value	Between *Q* (*p*-value)	Between I^2
Dominant	female	12	2661	984	– 0.07 (– 0.19 to 0.04)	33.86	0.20	0.06 (0.81)	0
	male	14	3251	1419	– 0.06 (– 0.13 to 0.01)	0.00	0.10		
	Old	20	4991	1859	– 0.10 (– 0.21 to 0.01)	53.50	0.09	0.35 (0.55)	0
	Young	12	1243	593	– 0.05 (– 0.16 to 0.06)	0.00	0.33		
	EUR	12	2451	1166	– 0.08 (– 0.17 to 0.01)	21.36	0.08	0.64 (0.42)	0
	EAS	13	3092	978	– 0.14 (– 0.30 to 0.01)	55.33	0.07		
	whole	19	2448	1164	– 0.03 (– 0.11 to 0.05)	10.09	0.44	3.97 (0.14)	49.66
	four_limbs	4	1628	483	– 0.15 (– 0.47 to 0.18)	70.22	0.25		
	lower_limbs	9	2229	942	– 0.24 (– 0.48 to 0.01)	60.32	0.06		
Recessive	female	12	850	2795	– 0.03 (– 0.13 to 0.07)	20.32	0.58	0.22 (0.64)	0
	male	14	1022	3648	0.01 (– 0.11 to 0.12)	39.53	0.90		
	Old	20	1539	5311	– 0.02 (– 0.15 to 0.12)	64.82	0.81	0.16 (0.69)	0
	Young	12	417	1419	0.02 (– 0.13 to 0.17)	23.93	0.75		
	EUR	12	693	2924	0.05 (– 0.06 to 0.16)	23.27	0.35	2.63 (0.11)	61.9
	EAS	13	1030	3040	– 0.08 (– 0.21 to 0.05)	49.13	0.22		
	whole	19	711	2901	0.03 (– 0.14 to 0.20)	56.99	0.71	2.11 (0.35)	5.29
	four_limbs	4	551	1560	– 0.09 (– 0.36 to 0.18)	57.83	0.38		
	lower_limbs	9	660	2511	– 0.15 (– 0.41 to 0.10)	67.29	0.20		
Additive	female	12	NA	NA	– 0.05 (– 0.14 to 0.04)	46.98	0.21	0.45 (0.50)	0
	male	14	NA	NA	– 0.02 (– 0.08 to 0.04)	39.98	0.51		
	Old	20	NA	NA	– 0.05 (– 0.13 to 0.03)	58.38	0.20	0.27 (0.61)	0
	Young	12	NA	NA	– 0.02 (– 0.12 to 0.08)	39.30	0.68		
	EUR	12	NA	NA	– 0.03 (– 0.11 to 0.06)	44.33	0.51	1.47 (0.23)	31.9
	EAS	13	NA	NA	– 0.10 (– 0.21 to 0.01)	64.59	0.07		
	whole	19	NA	NA	– 0.01 (– 0.07 to 0.06)	22.61	0.87	5.02 (0.08)	60.18
	four_limbs	4	NA	NA	– 0.09 (– 0.30 to 0.11)	73.34	0.25		
	lower_limbs	9	NA	NA	– 0.19 (– 0.39 to 0.01)	75.45	0.06		

The column headings represent the following: *k* is the number of included studies in the subgroup analysis. *n.e* and *n.c* represent the sample sizes for the experimental group (RX + XX genotype) and reference group (RR genotype), respectively. ES (95% CI) denotes the pooled effect size and its 95% confidence interval; this represents the standardized mean difference (SMD) for group comparisons or the beta coefficient (β) for the additive model (indicating the effect per copy of the minor allele). Positive SMD values favor the reference group, whereas negative values favor the experimental group. I^2 is the *I*-squared statistic for within-subgroup heterogeneity, reported as a percentage. The *p*-value indicates the statistical significance of the each subgroup's pooled effect. Between *Q* (*p*-value), and between I^2 indicate statistics for differences between subgroups

combined RX + XX genotypes exhibiting lower skeletal muscle mass compared with the RR genotype. Because moderate heterogeneity was observed across all genetic models, we examined whether the effects of the *ACTN3* polymorphism differed according to population characteristics and assessment methods. As a result, a trend toward a significant subgroup effect was observed among measurement-site categories. Meta-regression further suggested that the association of the X allele with lower skeletal muscle mass became more pronounced with increasing lower-limb specificity.

The findings of a significant association under the dominant model imply that even the heterozygous (RX) state may exhibit partial functional deficiency. Biologically, the *ACTN3* R577X polymorphism is a nonsense variant; individuals with the XX genotype lack α-actinin-3, whereas those with the RX genotype express it. Therefore, this variant is predicted to follow a recessive pattern. However, the observed data suggests that the functional impact may not be strictly recessive, indicating an intermediate phenotype for heterozygotes. Supporting this notion, studies using *Actn3* knockout mice suggest that the heterozygous genotype is associated with reduced muscle mass, accompanied by a significant reduction in muscle fiber diameter [57]. In humans, several studies have reported that the effects of *ACTN3* genotype may be additive. For example, a study comparing 40-m sprint time showed that the association between ACTN3 genotype and sprint performance was consistent with an additive model [58]. In addition, a meta-analysis examining the association between *ACTN3* gene polymorphism and flexibility reported a significant association only under the recessive model [59]. In present study, while the dominant model yielded significant results, the additive

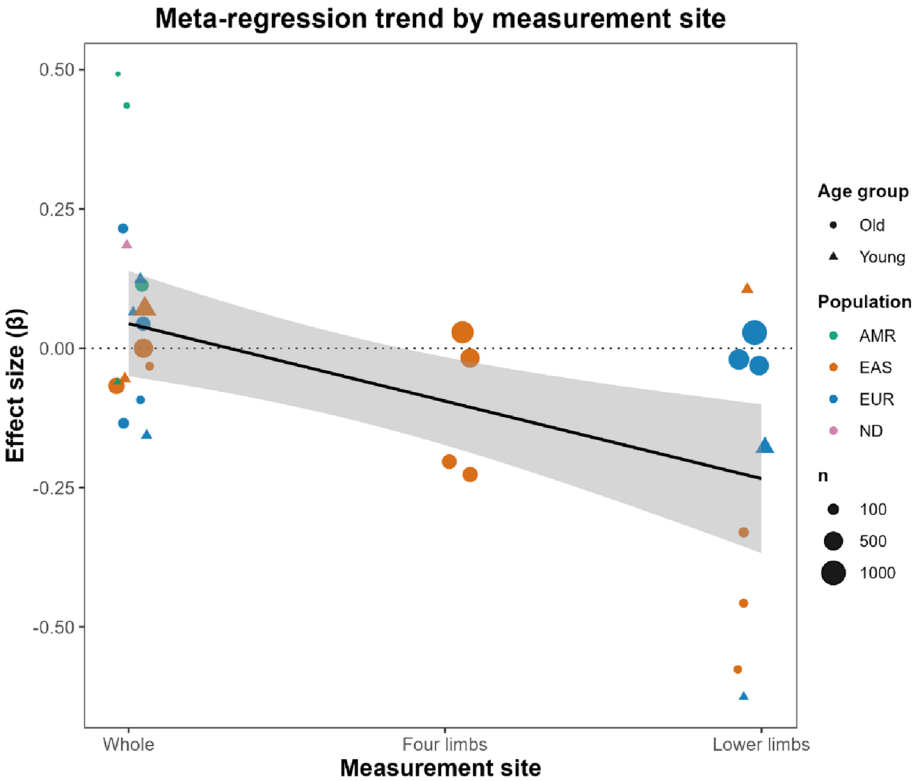


Fig. 5 Meta-regression of effect size according to measurement site. Measurement sites were coded as an ordinal variable reflecting increasing lower-limb specificity: whole body (0), four limbs (**1**), and lower limbs (**2**). Each point represents an independent dataset. Point size indicates sample size, color indicates ethnicity group, and shape indicates age group. The solid black line represents the fitted meta-regression line for measurement site, and the gray shaded area represents its 95% confidence interval. More negative effect sizes indicate a stronger association of the *ACTN3* R577X X allele with lower skeletal muscle mass

model showed only a trend. This pattern may indicate that the additive trend was partly driven by the RX genotype showing a phenotype closer to the XX genotype than to the RR genotype.

One possible mechanism through which the *ACTN3* R577X polymorphism may influence skeletal muscle mass is an increased vulnerability of muscle fiber structure resulting from reduced expression of α-actinin-3. Loss of α-actinin-3 due to the R577X variant is accompanied by compensatory upregulation of α-actinin-2, thereby preserving the total amount of actinin proteins [60]. However, this compensation appears insufficient to fully maintain structural integrity, potentially leading to reduced mechanical stability of muscle fibers. Consistent with this notion, studies in *Actn3* knockout mice have demonstrated greater muscle damage following eccentric contractions [60, 61]. Moreover, even under resting conditions, increased expression of Z-disk–associated proteins and the presence of centrally located nuclei have been observed, suggesting the presence of chronic muscle stress and ongoing remodeling processes [60]. Such persistent structural stress may impair satellite cell regenerative capacity through repeated cycles of muscle damage and regeneration, as has been reported in Duchenne muscular dystrophy, ultimately compromising the maintenance of muscle mass [62]. Therefore, sustained structural fragility resulting from the absence or reduction of α-actinin-3 may promote chronic muscle fiber damage and contribute to decreased skeletal muscle mass via impaired satellite cell–mediated regeneration. In addition, increased expression of Z-disk–related proteins, such as desmin and ZASP, has also been reported in heterozygous mice carrying the RX genotype [57]. This observation is consistent with the present findings, suggesting that the effects of the *ACTN3* polymorphism may already be evident in individuals carrying a single X allele.

Because previous studies have suggested that the effects of the *ACTN3* R577X polymorphism may differ between sexes [21, 23, 24], we examined the influence of genotype on skeletal muscle mass in male and female participants using subgroup analysis. However, when the available studies were quantitatively synthesized, no clear sex-specific difference in the genotype effect was observed.

A recent study using skeletal muscle from Actn3 knockout mice and human muscle biopsy samples reported that androgen receptor protein levels were lower in both Actn3 knockout mice and individuals with the XX genotype, irrespective of sex [63]. In contrast, studies using androgen receptor knockout mice have shown that the reduction in skeletal muscle mass caused by androgen receptor deficiency is evident in males, but not in females [64, 65]. These findings suggest that the effect mediated by reduced androgen receptor signaling may predominantly operate in males. In females, however, skeletal muscle mass may be more strongly influenced by female sex hormones, including estrogen. Notably, α-actinin-2 has been reported to interact not only with androgen receptor activity but also with estrogen receptor activity [66], suggesting that altered estrogen signaling may also contribute to reduced skeletal muscle mass. Therefore, the absence of a detectable sex difference in the present subgroup analysis may reflect distinct but convergent interactions between *ACTN3* genotype and sex hormone-related pathways in males and females. Further studies are needed to clarify these interactions, particularly the potential involvement of estrogen signaling.

In the subgroup analysis stratified by measurement site, a trend toward a significant subgroup effect was observed under the additive model. When we further examined whether the effect size varied linearly according to increasing lower-limb specificity, the model showed a significant linear fit. Specifically, the association of the X allele with reduced muscle mass became stronger as the measurement site became more specific to the lower limbs, suggesting that the effect of the X allele may be more pronounced in lower-limb measurements. This site-specific tendency may be related to impaired remodeling following the structural damage described above. Lower-limb muscles are repeatedly exposed to weight-bearing mechanical loads and eccentric contractions during daily activities [67, 68]. Therefore, reduced tolerance to mechanical stress caused by α-actinin-3 deficiency may be more likely to manifest over time as differences in damage repair and remodeling responses in lower-limb muscles. Although muscle mass is one of the major determinants of muscle strength, a meta-analysis examining the effect of *ACTN3* R577X on muscle strength did not show the lower-limb-specific effect observed in the present study [69]. One possible explanation for this discrepancy is that variation in the effect on muscle mass according to measurement site may not have been large enough to be detected as a clear site-specific difference in muscle strength, which is a complex phenotype. Muscle strength is determined not only by muscle mass but also by multiple factors, including muscle fiber-type composition, contractile properties, and neural control. *ACTN3* R577X, through α-actinin-3 deficiency, has been reported to reduce the proportion of Type IIx fibers, which generate high tension per unit cross-sectional area [24, 45]. Thus, changes in muscle fiber composition and muscle quality may have obscured the influence of site-specific variation in muscle mass when muscle strength was assessed as the outcome.

The linear effect across measurement sites did not explain the overall heterogeneity, and the other subgroup factors also did not show detectable subgroup effects when examined individually. These findings suggest that heterogeneity may reflect unexamined factors or the combined influence of multiple factors. Although the limited number of available datasets prevented us from statistically examining how combinations of multiple factors influence variability in the effect of *ACTN3* R577X (Fig. 5), which visualizes the study-level categories, suggests that the X allele may be associated with lower lower-limb muscle mass particularly in older East Asian populations. Further studies including diverse background populations are therefore warranted to clarify the influence of such combined factors. In particular, data on lower-limb muscle mass in young East Asian populations remain especially limited, and additional evidence from this group is needed to determine whether the apparent effect of the X allele on lower muscle mass is specific to older East Asian individuals.

In the present meta-analysis, the overall effect sizes were small, indicating that the contribution of the *ACTN3* genotype alone to skeletal muscle mass is limited and unlikely to represent a pathological phenotype associated with a substantially increased risk of sarcopenia. From an alternative perspective, the modestly lower muscle mass associated with the X allele may reflect a potentially rational and adaptive phenotype. Skeletal muscle is a primary site of energy expenditure during physical activity and is considered a metabolically costly tissue [70, 71]. Therefore, a slight reduction in muscle mass that does not impair activities of daily living could theoretically enhance whole-body energy efficiency and confer an advantage for survival. In line with this notion, a study of Spanish centenarians reported a potential contribution of the X allele to longevity [72]. Such an interpretation may provide a plausible evolutionary framework for understanding the signatures of selection at the *ACTN3* locus. Energy conservation is a critical factor for survival and reproduction. Previous studies have suggested that the X allele-associated shift toward a more aerobic muscle metabolism improves energetic efficiency and may have been advantageous during human evolution [15]. The modest reduction in muscle mass observed in the present analysis may be interpreted within a similar

evolutionary context. Nevertheless, further research is required to clarify the contribution of the X allele to natural selection.

Limitation

The number of available studies was limited, with data obtained from a total of 34 cohorts. We were unable to examine subgroup effects related to athlete status, sport participation, exercise habits, or physical activity levels because sufficient data for these factors could not be obtained. In particular, we did not identify any datasets that reported both skeletal muscle mass and *ACTN3* R577X genotype in athletes. Evaluating the potential modifying effects of physical activity levels, athlete status, and training history on the association between *ACTN3* R577X and skeletal muscle mass may be important because previous studies have suggested that individuals with the XX genotype may show attenuated training-induced muscle adaptations, potentially through reduced activation of hypertrophy-related pathways such as mTORC1 signaling [73, 74]. In the present study, only baseline skeletal muscle mass was extracted from intervention studies; therefore, genotype-related differences that may emerge after training or in highly trained populations could not be captured.

Furthermore, multiple cohorts were extracted from the same studies. Although we confirmed in the Methods section that there was no overlap of participants, data derived from the same study inevitably share the same study design and data collection methods. Thus, the cohorts cannot be regarded as completely independent, and this may have influenced the pooled estimates. Finally, different measurement methods for skeletal muscle mass were included. The present meta-analysis incorporated data assessed by fat-free mass, muscle volume, and cross-sectional area. To integrate these heterogeneous measures, standardized mean differences were calculated based on the standard deviation of each dataset. Therefore, the results should be interpreted with caution, because the effect size reflects relative differences standardized by variability among studies, rather than absolute differences in skeletal muscle mass.

Conclusion

This meta-analysis suggests that the *ACTN3* R577X polymorphism is associated with skeletal muscle mass and that this effect may be detectable even in heterozygous individuals. However, the magnitude of this association was very small. Differences in measurement sites were suggested to modulate the effect of *ACTN3* R577X on skeletal muscle mass; however, measurement site alone did not substantially explain the observed heterogeneity. Similarly, none of the other factors examined in the present study, including sex, age, and ethnicity, substantially explained the variability in the effect of *ACTN3* R577X when assessed as a single factor. The remaining heterogeneity may reflect the combined influence of multiple background characteristics or factors not examined in the present study. Therefore, future studies should aim to collect data from diverse populations while carefully considering differences in background characteristics.

Abbreviations

SMD	Standardized mean difference
LBM	Lean body mass
FFM	Fat-free mass
CSA	Muscle cross-sectional area
BIA	Bioelectrical impedance analysis
DEXA	Dual-energy X-ray absorptiometry
MRI	Magnetic resonance imaging
EUR	European
EAS	East Asian
AMR	Admixed American

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40101-026-00439-5.

Additional file 1: Traffic light plot presenting the risk of bias judgments for each included study across all domains. Green, yellow, and red indicate low, unclear, and high risk of bias, respectively. The RoBANS 2 tool includes eight domains for assessing risk of bias: comparability of the target group (D1), target group selection (D2), confounders (D3), measurement of exposure (D4), blinding of assessors (D5), outcome assessment (D6), incomplete outcome data (D7), and selective outcome reporting (D8). Studies labeled with lowercase letters (a, b, c) indicate different subgroups (e.g., sex-specifi c cohorts) derived from the same original study. Summary plot showing the proportion of studies rated as low, unclear, or high risk of bias for each domain.

Additional file 2: The dotted line indicates the pooled effect size, and the shaded areas represent significance contours.

Additional file 3.

Acknowledgements

Not applicable.

Authors' contributions

Conceptualization: S.H. and K.N. Study design: S.H., M.K. and N.K. Screening and Data extraction: S.H. and M.K. Data analysis: S.H. Project administration and Supervision: K.N. Writing—original draft: S.H. Writing—review and editing: M.K., N.K., and K.N. All authors read and approved the final manuscript.

Funding

This project was funded through institutional support from the Nippon Sport Science University.

Data availability

The datasets and R scripts generated during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 30 January 2026 Accepted: 20 July 2026
Published online: 27 July 2026

References

1. Kim G, Kim JH. Impact of skeletal muscle mass on metabolic health. Endocrinol Metab. 2020;35:1–6. https://doi.org/10.3803/EnM.2020.35.1.1.
2. Merz KE, Thurmond DC. Role of skeletal muscle in insulin resistance and glucose uptake. Compr Physiol. 2020;10:785–809. https://doi.org/10.1002/cphy.c190029.
3. Hoffmann C, Weigert C. Skeletal muscle as an endocrine organ: the role of myokines in exercise adaptations. Cold Spring Harb Perspect Med. 2017;7:a029793. https://doi.org/10.1101/cshperspect.a029793.
4. Argilés JM, Campos N, Lopez-Pedrosa JM, Rueda R, Rodriguez-Mañas L. Skeletal muscle regulates metabolism via interorgan crosstalk: roles in health and disease. J Am Med Dir Assoc. 2016;17:789–96. https://doi.org/10.1016/j.jamda.2016.04.019.
5. Wolfe RR. The underappreciated role of muscle in health and disease2. Am J Clin Nutr. 2006;84:475–82. https://doi.org/10.1093/ajcn/84.3.475.
6. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MAE, den Braver NR, Berkhof J, Langius JAE, et al. Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. J Clin Oncol. 2016;34:1339–44. https://doi.org/10.1200/JCO.2015.63.6043.
7. Miyamoto Y, Baba Y, Sakamoto Y, Ohuchi M, Tokunaga R, Kurashige J, et al. Sarcopenia is a negative prognostic factor after curative resection of colorectal cancer. Ann Surg Oncol. 2015;22:2663–8. https://doi.org/10.1245/s10434-014-4281-6.
8. Pin F, Couch ME, Bonetto A. Preservation of muscle mass as a strategy to reduce the toxic effects of cancer chemotherapy on body composition. Curr Opin Support Palliat Care. 2018;12:420–6. https://doi.org/10.1097/SPC.0000000000000382.
9. Forbes GB, Sauer EP, Weitkamp LR. Lean body mass in twins. Metabolism. 1995;44:1442–6. https://doi.org/10.1016/0026-0495(95)90144-2.
10. Seeman E, Hopper JL, Young NR, Formica C, Goss P, Tsalamandris C. Do genetic factors explain associations between muscle strength, lean mass, and bone density? A twin study. Am J Physiol. 1996;270:E320-327. https://doi.org/10.1152/ajpendo.1996.270.2.E320.
11. Arden NK, Spector TD. Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. J Bone Miner Res. 1997;12:2076–81. https://doi.org/10.1359/jbmr.1997.12.12.2076.
12. Loos R, Thomis M, Maes HH, Beunen G, Claessens AL, Derom C, et al. Gender-specific regional changes in genetic structure of muscularity in early adolescence. J Appl Physiol. 1985;82:1802–10. https://doi.org/10.1152/jappl.1997.82.6.1802.
13. Thomis MA, Van Leemputte M, Maes HH, Blimkie CJR, Claessens AL, Marchal G, et al. Multivariate genetic analysis of maximal isometric muscle force at different elbow angles. J Appl Physiol Am Physiol Soc. 1997;82:959–67. https://doi.org/10.1152/jappl.1997.82.3.959.
14. Aslam MA, Ma EB, Huh JY. Pathophysiology of sarcopenia: genetic factors and their interplay with environmental factors. Metabolism. 2023;149:155711. https://doi.org/10.1016/j.metabol.2023.155711.
15. MacArthur DG, Seto JT, Raftery JM, Quinlan KG, Huttley GA, Hook JW, et al. Loss of *ACTN3* gene function alters mouse muscle metabolism and shows evidence of positive selection in humans. Nat Genet. 2007;39:1261–5. https://doi.org/10.1038/ng2122.
16. MacArthur DG, Seto JT, Chan S, Quinlan KGR, Raftery JM, Turner N, et al. An Actn3 knockout mouse provides mechanistic insights into the association between alpha-actinin-3 deficiency and human athletic performance. Hum Mol Genet. 2008;17:1076–86. https://doi.org/10.1093/hmg/ddm380.
17. Garton FC, Seto JT, Quinlan KGR, Yang N, Houweling PJ, North KN. α-Actinin-3 deficiency alters muscle adaptation in response to denervation and immobilization. Hum Mol Genet. 2014;23:1879–93. https://doi.org/10.1093/hmg/ddt580.
18. Seto J, Roeszler K, Meehan L, Wood H, Tiong C, Bek L, et al. ACTN3 genotype influences skeletal muscle mass regulation and response to dexamethasone. Sci Adv. 2021;7:eabg0088. https://doi.org/10.1126/sciadv.abg0088.
19. Zempo H, Tanabe K, Murakami H, Iemitsu M, Maeda S, Kuno S. *ACTN3* polymorphism affects thigh muscle area. Int J Sports Med. 2010;31:138–42. https://doi.org/10.1055/s-0029-1242808.
20. Delmonico MJ, Zmuda JM, Taylor BC, Cauley JA, Harris TB, Manini TM, et al. Association of the ACTN3 genotype and physical functioning with age in older adults. J Gerontol A Biol Sci Med Sci. 2008;63:1227–34. https://doi.org/10.1093/gerona/63.11.1227.
21. Seto JT, Chan S, Turner N, MacArthur DG, Raftery JM, Berman YD, et al. The effect of α-actinin-3 deficiency on muscle aging. Exp Gerontol. 2011;46:292–302. https://doi.org/10.1016/j.exger.2010.11.006.
22. Zempo H, Tanabe K, Murakami H, Iemitsu M, Maeda S, Kuno S. Age differences in the relation between *ACTN3* R577X polymorphism and thigh-muscle cross-sectional area in women. Genet Test Mol Biomarkers. 2011;15:639–43. https://doi.org/10.1089/gtmb.2011.0005.
23. Ma T, Lu D, Zhu Y-S, Chu X-F, Wang Y, Shi G-P, et al. ACTN3 genotype and physical function and frailty in an elderly Chinese population: the Rugao Longevity and Ageing Study. Age Ageing. 2018;47:416–22. https://doi.org/10.1093/ageing/afy007.
24. Kumagai H, Tobina T, Ichinoseki-Sekine N, Kakigi R, Tsuzuki T, Zempo H, et al. Role of selected polymorphisms in determining muscle fiber composition in Japanese men and women. J Appl Physiol. 1985;124:1377–84. https://doi.org/10.1152/japplphysiol.00953.2017.
25. Munir A, Che Muhamed A, Ahmad Yusof H, Singh R, Zafarina Z, Rooney K. Alpha-Actinin-3 (ACTN3) R/X gene polymorphism and physical performance of multi-ethnic Malaysian population. 2016:2322–3537.
26. Oliveira E, Rodrigues P, Salgueirosa F, Seniski G, Wharton L, Osiecki R. Effect of ACTN3 R577X genotypes on muscle strength and power in Brazilian mixed martial arts athletes. J Exerc Physiol Online. 2018;21:202.
27. Friedlander SM, Herrmann AL, Lowry DP, Mepham ER, Lek M, North KN, et al. ACTN3 allele frequency in humans covaries with global latitudinal gradient. PLoS ONE. 2013;8:e52282. https://doi.org/10.1371/journal.pone.0052282.
28. Amorim CEG, Acuña-Alonzo V, Salzano FM, Bortolini MC, Hünemeier T. Differing evolutionary histories of the ACTN3*R577X polymorphism among the major human geographic groups. PLOS ONE. Public Library Sci. 2015;10:e0115449. https://doi.org/10.1371/journal.pone.0115449.
29. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5:210. https://doi.org/10.1186/s13643-016-0384-4.
30. Seo H-J, Kim SY, Lee YJ, Park J-E. RoBANS 2: a revised risk of bias assessment tool for nonrandomized studies of interventions. Korean J Fam Med. 2023;44:249–60. https://doi.org/10.4082/kjfm.23.0034.
31. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34. https://doi.org/10.1136/bmj.315.7109.629.
32. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing meta-analysis with R: a hands-on guide. 1st ed. Boca Raton, FL and London: Chapman & Hall/CRC Press; 2021.
33. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58. https://doi.org/10.1002/sim.1186.
34. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. 2nd edition. Hoboken, NJ: Wiley-Blackwell; 2019.
35. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2020;372:n71. https://doi.org/10.1136/bmj.n71.

36. Boshnjaku A, Krasniqi E, Tschan H, Wessner B. ACTN3 genotypes and their relationship with muscle mass and function of Kosovan adults. Int J Environ Res Public Health. 2021;18:9135. https://doi.org/10.3390/ijerph18179135.
37. Cho J, Lee I, Kang H. ACTN3 gene and susceptibility to sarcopenia and osteoporotic status in older Korean adults. BioMed Res Int. 2017;2017:1–8. https://doi.org/10.1155/2017/4239648.
38. Kiuchi Y, Makizako H, Nakai Y, Taniguchi Y, Tomioka K, Sato N, et al. Associations of alpha-actinin-3 genotype with thigh muscle volume and physical performance in older adults with sarcopenia or pre-sarcopenia. Exp Gerontol. 2021;154:111525. https://doi.org/10.1016/j.exger.2021.111525.
39. Broos S, Van Leemputte M, Deldicque L, Thomis MA. History-dependent force, angular velocity and muscular endurance in ACTN3 genotypes. Eur J Appl Physiol. 2015;115:1637–43. https://doi.org/10.1007/s00421-015-3144-6.
40. Lima R, Leite T, Pereira R, Rabelo H, Roth S, Oliveira R. *ACE* and *ACTN3* genotypes in older women: muscular phenotypes. Int J Sports Med. 2011;32:66–72. https://doi.org/10.1055/s-0030-1267229.
41. Min S-K, Lim S-T, Kim C-S. Association of ACTN3 polymorphisms with BMD, and physical fitness of elderly women. J Phys Ther Sci. 2016;28:2731–6. https://doi.org/10.1589/jpts.28.2731.
42. Erskine RM, Williams AG, Jones DA, Stewart CE, Degens H. The individual and combined influence of ***ACE*** and ***ACTN3*** genotypes on muscle phenotypes before and after strength training. Scand J Med Sci Sports. 2014;24:642–8. https://doi.org/10.1111/sms.12055.
43. Urzi F, Pokorny B, Buzan E. Pilot study on genetic associations with age-related sarcopenia. Front Genet. 2021;11:615238. https://doi.org/10.3389/fgene.2020.615238.
44. Clarkson PM, Devaney JM, Gordish-Dressman H, Thompson PD, Hubal MJ, Urso M, et al. ACTN3 genotype is associated with increases in muscle strength in response to resistance training in women. J Appl Physiol. 2005;99:154–63. https://doi.org/10.1152/japplphysiol.01139.2004.
45. Vincent B, De Bock K, Ramaekers M, Van den Eede E, Van Leemputte M, Hespel P, et al. ACTN3 (R577X) genotype is associated with fiber type distribution. Physiol Genomics Am Physiol Soc. 2007;32:58–63. https://doi.org/10.1152/physiolgenomics.00173.2007.
46. Walsh S, Liu D, Metter EJ, Ferrucci L, Roth SM. *ACTN3* genotype is associated with muscle phenotypes in women across the adult age span. J Appl Physiol. 2008;105:1486.
47. Norman B, Esbjörnsson M, Rundqvist H, Österlund T, Von Walden F, Tesch PA. Strength, power, fiber types, and mRNA expression in trained men and women with different *ACTN3* R577X genotypes. J Appl Physiol. 2009;106:959–65. https://doi.org/10.1152/japplphysiol.91435.2008.
48. McCauley T, Mastana SS, Folland JP. ACE I/D and ACTN3 R/X polymorphisms and muscle function and muscularity of older Caucasian men. Eur J Appl Physiol. 2010;109:269–77. https://doi.org/10.1007/s00421-009-1340-y.
49. Hanson ED, Ludlow AT, Sheaff AK, Park J, Roth SM. *ACTN3* genotype does not influence muscle power. Int J Sports Med. 2010;31:834–8. https://doi.org/10.1055/s-0030-1263116.
50. Abudurezake A, Kakehi S, Umemura F, Kaga H, Someya Y, Tabata H, et al. Masseter muscle volume, sarcopenia, and muscle determinants: insights from ACTN3 polymorphism in elderly Japanese in the Bunkyo Health Study. Arch Med Res. 2025;56:103095. https://doi.org/10.1016/j.arcmed.2024.103095.
51. Iwasaka C, Nanri H, Hara M, Nishida Y, Shimanoe C, Yamada Y, et al. Interaction between habitual green tea and coffee consumption and ACTN3 genotype in association with skeletal muscle mass and strength in middle-aged and older adults. J Frailty Aging. 2024;13:267–75. https://doi.org/10.14283/jfa.2024.3.
52. da Silva AC, Mapa V, Ferreira-Júnior JB, de Oliveira EC, Becker LK, Rosse I, et al. Progressive strength training can reverse sarcopenia stage in middle-aged and older adults regardless of their genetic profile. Arch Gerontol Geriatr. 2024;117:105182. https://doi.org/10.1016/j.archger.2023.105182.
53. Shin S. Association of genotype, high-G tolerance, and body composition in jet aircraft aviators. Mil Med. 2024;189:486–92. https://doi.org/10.1093/milmed/usad248.
54. Taniguchi Y, Makizako H, Nakai Y, Kiuchi Y, Akaida S, Tateishi M, et al. Associations of the alpha-actinin three genotype with bone and muscle mass loss among middle-aged and older adults. J Clin Med. 2022;11:6172. https://doi.org/10.3390/jcm11206172.
55. Güereca-Arvizuo J, Hernández-Torres P, Moreno-Brito V, Sierra-Muñiz G, Trejo-Trejo M, Cervantes-Borunda M, et al. Muscle power and blood lactate kinetics in ACTN3 genotypes. Int J Med Sci Phys Act Sport Rev Int Med Cienc Act Física Deporte. 2022;22:215–28. https://doi.org/10.15366/rimcafd2022.86.001.
56. Shang X, Zhang F, Zhang L, Huang C. ACTN3 R577X polymorphism and performance phenotypes in young Chinese male soldiers. J Sports Sci. 2012;30:255–60. https://doi.org/10.1080/02640414.2011.619203.
57. Hogarth MW, Garton FC, Houweling PJ, Tukiainen T, Lek M, Macarthur DG, et al. Analysis of the ACTN3 heterozygous genotype suggests that α-actinin-3 controls sarcomeric composition and muscle function in a dose-dependent fashion. Hum Mol Genet. 2016;25:866–77. https://doi.org/10.1093/hmg/ddv613.
58. Moran CN, Yang N, Bailey MES, Tsiokanos A, Jamurtas A, MacArthur DG, et al. Association analysis of the ACTN3 R577X polymorphism and complex quantitative body composition and performance phenotypes in adolescent Greeks. Eur J Hum Genet. 2007;15:88–93. https://doi.org/10.1038/sj.ejhg.5201724. Nature Publishing Group.
59. Saito A, Saito M, de Almeida KY, Homma H, Deguchi M, Kozuma A, et al. The association between the ALDH2 rs671 polymorphism and athletic performance in Japanese power and strength athletes. Genes. 2022;13:1735. https://doi.org/10.3390/genes13101735. Multidisciplinary Digital Publishing Institute.
60. Seto JT, Lek M, Quinlan KGR, Houweling PJ, Zheng XF, Garton F, et al. Deficiency of α-actinin-3 is associated with increased susceptibility to contraction-induced damage and skeletal muscle remodeling. Hum Mol Genet. 2011;20:2914–27. https://doi.org/10.1093/hmg/ddr196.
61. Haug M, Reischl B, Nübler S, Kiriaev L, Mázala DAG, Houweling PJ, et al. Absence of the Z-disc protein α-actinin-3 impairs the mechanical stability of Actn3KO mouse fast-twitch muscle fibres without altering their contractile properties or twitch kinetics. Skelet Muscle. 2022;12:14. https://doi.org/10.1186/s13395-022-00295-8.
62. Careccia G, Mangiavini L, Cirillo F. Regulation of satellite cells functions during skeletal muscle regeneration: a critical step in physiological and pathological conditions. Int J Mol Sci. 2024;25:512. https://doi.org/10.3390/ijms25010512. Multidisciplinary Digital Publishing Institute.
63. Roeszler KN, See M, Meehan LR, Lima G, Kolliari-Turner A, Alexander SE, et al. *ACTN3* genotype influences androgen response in developing murine skeletal muscle. Sci Adv. 2025;11:eadw1059. https://doi.org/10.1126/sciadv.adw1059.
64. MacLean HE, Chiu WSM, Notini AJ, Axell A-M, Davey RA, McManus JF, et al. Impaired skeletal muscle development and function in male, but not female, genomic androgen receptor knockout mice. FASEB J. 2008;22:2676–89. https://doi.org/10.1096/fj.08-105726.
65. Fagman JB, Wilhelmson AS, Motta BM, Pirazzi C, Alexanderson C, De Gendt K, et al. The androgen receptor confers protection against diet-induced atherosclerosis, obesity, and dyslipidemia in female mice. FASEB J. 2015;29:1540–50. https://doi.org/10.1096/fj.14-259234.
66. Huang SM, Huang CJ, Wang WM, Kang JC, Hsu WC. The enhancement of nuclear receptor transcriptional activation by a mouse actin-binding protein, alpha actinin 2. J Mol Endocrinol BioScientifica. 2004;32:481–96. https://doi.org/10.1677/jme.0.0320481.
67. Hu X, Pickle NT, Grabowski AM, Silverman AK, Blemker SS. Muscle eccentric contractions increase in downhill and high-grade uphill walking. Front Bioeng Biotechnol. 2020;8. https://doi.org/10.3389/fbioe.2020.573666. Cited 2026 June 12. Frontiers.
68. Cvečka J, Vajda M, Novotná A, Löfler S, Hamar D, Krčmár M. Benefits of eccentric training with emphasis on demands of daily living activities and feasibility in older adults: a literature review. Int J Environ Res Public Health. 2023;20:3172. https://doi.org/10.3390/ijerph20043172. Multidisciplinary Digital Publishing Institute.
69. Kamiya-Saito M, Zempo H, de Almeida KY, Homma H, Mochizuki Y, Deguchi M, et al. Association of the *ACTN3* genotype with muscle function: a systematic review and meta-analysis. Int J Sports Med. 2026. https://doi.org/10.1055/a-2799-1026.
70. Hargreaves M, Spriet LL. Skeletal muscle energy metabolism during exercise. Nat Metab. 2020;2:817–28. https://doi.org/10.1038/s42255-020-0251-4. Nature Publishing Group.

71. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metab. 2013;17:162–84. https://doi.org/10.1016/j.cmet.2012.12.012.
72. Fiuza-Luces C, Ruiz JR, Rodríguez-Romo G, Santiago C, Gómez-Gallego F, Yvert T, et al. Are 'endurance' alleles 'survival' alleles? Insights from the ACTN3 R577X Polymorphism. PLOS ONE. 2011;6:e17558. https://doi.org/10.1371/journal.pone.0017558. Public Library of Science.
73. Gentil P, Pereira RW, Leite TKM, Bottaro M. ACTN3 R577X polymorphism and neuromuscular response to resistance training. J Sports Sci Med. 2011;10:393–9.
74. Norman B, Esbjörnsson M, Rundqvist H, Österlund T, Glenmark B, Jansson E. *ACTN3* genotype and modulation of skeletal muscle response to exercise in human subjects. J Appl Physiol. 2014;116:1197–203. https://doi.org/10.1152/japplphysiol.00557.2013.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.