SP1 (*rs1800012*) in anterior cruciate ligament injuries

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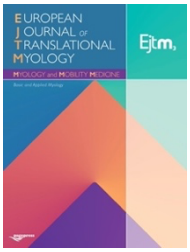

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The role of *SP1* (*rs1800012*) in anterior cruciate ligament injuries: updated meta-analysis

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Abstract

The Anterior Cruciate Ligament (ACL) is vital for knee stability, and its rupture is a major orthopedic concern with significant health and economic impacts. Evidence suggests a substantial hereditary component in ACL injury susceptibility, with the *COL1A1 rs1800012* (*SP1*) polymorphism frequently studied but with inconsistent results. To clarify the association between the *rs1800012* in *COL1A1* and ACL injury risk, this meta-analysis synthesized data from case-control and cohort studies focusing exclusively on ACL injuries. Systematic searches of PubMed, Embase, Web of Science, and Scopus identified studies up to June 2025. Eligible studies included individuals diagnosed with ACL injuries and healthy controls, reporting genotype frequencies for *rs1800012*. Pooled Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated for various genetic models using random-effects meta-analysis. Study quality was assessed via the Newcastle–Ottawa Scale, and publication bias and heterogeneity were evaluated. Nine studies (1,171 cases, 2,005 controls) were included. The TT genotype was significantly protective under the recessive model (TT *vs*. TG+GG: OR = 0.49, 95% CI: 0.25–0.97, $p = 0.041$), and also in direct genotype comparisons (TT *vs*. TG: OR = 0.41, 95% CI: 0.21–0.80, $p = 0.009$). Conversely, the TG genotype increased ACL injuries risk under the overdominant

model (TG vs. TT+GG: OR = 1.28, 95% CI: 1.07–1.52, $p = 0.006$) and when compared to GG (TG *vs*. GG: OR = 1.24, 95% CI: 1.05–1.48, $p = 0.014$). No significant associations were observed under the allele contrast (T *vs*. G: OR = 1.04, 95% CI: 0.90–1.21, $p = 0.61$) or dominant models (TT+TG *vs*. GG: OR = 1.15, 95% CI: 0.97–1.37, $p = 0.10$). Heterogeneity was consistently low, and sensitivity analyses confirmed the robustness of these findings. No evidence of publication bias was detected. This meta-analysis demonstrates genotype-specific effects of *rs1800012* on ACL injuries risk: the TT genotype is protective, while the TG genotype confers increased risk.

Keywords: *COL1A1*; rs1800012; anterior cruciate ligament rupture; genetic susceptibility; sports injury genetics.

The Anterior Cruciate Ligament (ACL) is a collagenous structure composed of water, fibrocartilaginous proteins, and collagen fibrils, which collectively enhance its mechanical integrity and capacity to withstand biomechanical loads. The ACL serves as the fundamental mechanical barrier to excessive anterior tibial translation. It withstands excessive external rotation and varus-valgus stresses of the knee, particularly during weight-bearing physical activity, making ACL a vital function in knee joint. Subsequently, ACL injuries result in significant joint instability and damage to intra-articular structures.[1,2] ACL injuries represent more than half of knee injuries and impact more than 200,000 individuals annually in the United States.[3] ACL injuries have a significant economic impact, resulting in substantial financial losses for athletes and teams. For instance, the National Basketball Association has incurred a cumulative loss of $99 million, and the National Football League has experienced over $2 million in lost earnings per injured player. Additionally, these injuries commonly lead to psychological challenges such as depression, anxiety, and a reduced sense of capability, especially during recovery and return to sport.[4] ACL injuries have a multifactorial nature influenced by the interplay of extrinsic and intrinsic factors, such as hormonal levels and hereditary vulnerability.[5]

A growing body of evidence indicates that heredity plays a significant role in ACL injury susceptibility. Indeed, several familial, twin, and genetic association studies have reported that heredity has a

considerable involvement in ACL injuries and tears. For instance, a case–control study reported that individuals who suffered an ACL tear were at a higher risk of having a first-degree relative with a history of ACL injuries compared to those without injury.[6,7] A large twin study found that genetic factors account for about 70% of ACL injury risk, indicating that nearly two-thirds of the intraindividual differences in ACL injury risk can be attributed to genetic factors.[8] However, this condition is a polygenic trait influenced by several genetic loci involving gene variants in structural genes or genes involved in ligament repair.[9] For instance, genetic association studies have identified numerous candidate genes, such as *COL1A1*, *COL5A1*, *COL12A1*, *COL14A1*, *DCN*, *ACAN*, and *VEGFA*.[6,10] Notably, collagen-encoding genes represent most candidate genes due to their significant role in ACL biology. Nevertheless, these findings, combined with environmental factors, increase the complexity of ACL injury. Understanding the genetic contribution, particularly collagen-encoding genes, is a significant epidemiologic aspiration. A comprehensive understanding of these risk factors will enable physicians to identify persons at elevated risk before they consult with an orthopedic surgeon.[9]

Collagen Type I represents a predominant component in ACL and plays a crucial structural function; structural and/or quantitative alterations in collagen type I might lead to ACL weakening or strengthening.[11] Collagen fibers constitute about 75% of the dry weight of the ACL, with type I being primarily responsible for the ligament's tensile strength and load-bearing capacity.[12,13] These type I collagen fibers are organized into bundles aligned along the ligament's axis, forming the fundamental framework that allows the ACL to withstand high tensile forces and resist excessive joint motion. The fibers are cross-linked and interwoven with other matrix components, conferring additional toughness and some viscoelasticity to the tissue. This hierarchical structure gives the ACL its superior mechanical properties and anisotropy.[14] collagen I exists as a heterotrimer, encompassing two α1 chains (encoded by *COL1A1*) and one α2 chain (encoded by *COL1A2*). Nonetheless, a minor quantity of collagen I homotrimers (three molecules of α1 chains) exists in adult cutaneous and fetal tissue, which negatively impacts self-assembling fibril properties while also enhancing resistance to proteases.[15] Additionally, the homotrimers form is characterized by having lower tensile strength and an increased lateral space due to weaker intermolecular interactions.[16,17]

Sp1 binding site polymorphism (*rs1800012*) in the *COL1A1* gene involves the substitution of G to T in the fourth binding site at intron 1. This variant has been reported to alter binding site affinity, boosting *COL1A1* expression, leading to increased α1 chain production and distributing the α1/α2 ratio. This

increases the probability of assembling a homotrimer (comprising three identical α1) rather than the typical heterotrimer. This increases the possibility of assembling a homotrimer rather than the typical heterotrimer.[18–21] This polymorphism has been implicated in impacting a wide range of disorders, including ligament-related conditions.[22] Numerous studies have investigated the association between *rs1800012* and ACL injuries across multiple populations. However, the data demonstrate inconsistent findings, while some studies reported a lack of association,[5,10,23] while others reported that TT genotype is a protective factor.[24,25] Notably, the minor T-allele frequencies exhibit a significant difference between different ethnic groups, which may partly explain the inconsistent results.[26] Several previous meta-analyses have investigated the impact of the *rs1800012* polymorphism; however, these studies have pooled data from diverse ligament injuries, including but not limited to ACL injuries, as well as other soft tissue pathologies.[27,28] Such pooling of heterogeneous pathological phenotypes may obscure or dilute associations specific to ACL injury, given the differences in anatomical structure, mechanical loading, and injury mechanisms among tissues.[29,30] To date, no meta-analysis has exclusively focused on evaluating the association between *rs1800012* and ACL injuries. Therefore, the present study aims to clarify this relationship by synthesizing available evidence specifically on ACL injuries, thereby providing a more accurate and targeted assessment of the genetic contribution of the *rs1800012* variant to ACL injury risk.

Materials and Methods

Literature search

This meta-analysis was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[31] The PROSPERO registration number and the published protocol were CRD420251071241. Studies examining the association between the *rs1800012* polymorphism in CLO1A1 with ACL rupture or tear risk were included for searching PUBBMED, EMPASE, WEB OF SCIENCE, AND SCOPUS prior June 14th,2025 using the following terms: ("*COL1A1*" OR "collagen type I alpha 1") AND ("*SP1*" OR "*rs1800012*") AND ("*ACL*" OR "*anterior cruciate ligament*") AND ("rupture" OR "tear" OR "injury") AND ("polymorphism" OR "genotype" OR "variant"). To avoid overlooking potentially relevant studies, we meticulously reviewed the reference lists of the obtained original articles, together with previously published reviews and meta-

analyses. The search will not be limited by language or data type, but only full-text English articles will be considered.

Inclusion and exclusion criteria

Related studies should follow these criteria: i) following population standards, participants in case-control or cohort studies assessing the *rs1800012* polymorphism should include individuals diagnosed with ACL rupture, regardless of age, sex, or ethnicity, along with healthy controls who have no history of ACL injury; ii) in line with exposure and intervention parameters, included studies must confirm the presence of the *rs1800012* polymorphism in the *COL1A1* gene, and validated molecular techniques must be used for genotyping; iii) studies should report genotype or allele frequency (GG, GT, TT) in those with ACL injuries and healthy controls; iv) however, studies were excluded if they addressed non-ACL ligament disorders, involved participants with prior ACL surgeries, lacked *rs1800012* polymorphism genetic data, lacked genotype frequency details, or focused only on interventions such as rehabilitation and surgeries rather than genetic exposure.

Data extraction and quality assessment

Each eligible study provided the following extracted variables: Study ID, year of publication, country, ethnicity, case characteristics, diagnostic and genotyping methods, age and gender of participants, control group source, sample size, and genotype/allele frequencies. Risk of bias was calculated, and studies were chosen based on their quality, which was assessed using the Newcastle-Ottawa Scale (NOS). The NOS scale ranges from 0 to 9; scores of 6 and above indicate a high-quality study.[32] The processes of literature screening, identifying eligible studies, extracting data, and assessing quality were independently performed by two reviewers, and disagreements were settled by consulting a third investigator.

Statistical analysis

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Meta-analyses were conducted using a random-effects model and fixed-effects model through the web tool Metagenyo.[33] Odds ratios and 95% [confidence intervals (CL)] will be calculated for Allele contrast (T VS G), Recessive model (TT vs TG + GG), Dominant model (TT+TG vs GG), and Overdominant model (TG vs TT +GG). Subgroup analyses (e.g., by ethnicity) and sensitivity analyses (e.g., excluding studies at high risk of bias or with data anomalies) will be conducted where appropriate. Additionally, heterogeneity will be assessed using the I^2 statistic and Cochran's Q test. If sufficient studies are available, publication bias will be evaluated using funnel plots and Egger's test. All analyses will be performed using appropriate statistical software.

Results

Study selection and characteristics

A total of 358 records were detected through the data source searches in Embase, PubMed, Scopus, and Web of Science. A total of 270 abstracts were reviewed for relevance after removing the duplicates, leading to the exclusion of 247 abstracts based on their titles and abstracts. 23 articles full text were then assessed for their suitability. Of the total, 14 studies were excluded due to the following factors: only the abstract was available in English (n = 4), the study investigated *COL1A1* gene variants other than *rs1800012* (n = 6) , focus was on ligament injuries other than ACL (n = 2) , or there were concerns regarding data quality, such as genotype or allele labeling errors (n = 1).[34] There were no additional related studies documented through the reference lists. Ultimately, only nine studies met the eligibility criteria and were included in this meta-analysis. The detailed process of study is presented in Figure 1.

Study characteristics and Hardy–Weinberg equilibrium

The characteristics of the nine studies included in this meta-analysis are provided in Supplementary Table S1. encompassing a total of 1171 cases and 2005 controls. The majority of studies were performed in Caucasian populations with additional representation from Indian and Han Chinese populations. Most studies utilized a case–control design, with cases typically defined as individuals with surgically or clinically confirmed ACL ruptures, while controls were healthy individuals without a

history of ACL injury. Several studies focused on specific populations such as recreational skiers, professional athletes, or elite female athletes, thereby contributing to the diversity in participant backgrounds. Diagnostic methods primarily involved surgical, arthroscopic, or Magnetic Resonance Imaging (MRI) confirmation of ACL rupture, ensuring diagnostic consistency and reliability. Genotyping methods varied across studies and included TaqMan genotyping assays, allele-specific PCR, solid-phase minisequencing, allelic discrimination, and Restriction Fragment Length Polymorphism (RFLP) PCR.

Genotype distributions and allele frequencies for the *rs1800012* were reported for all included studies. The Hardy–Weinberg Equilibrium (HWE) was assessed in control groups for each study. All studies, except for Zhao *et al*.,[23] demonstrated genotype distributions consistent with HWE in controls ($p > 0.05$ by chi-squared test). The Zhao et al. study deviated from HWE ($p = 0$), which may reflect underlying population structure, technical issues, or other biases.

Risk of bias/quality assessment

The quality of the nine studies included in this analysis was assessed using the NOS, as shown in Table 1. Scores ranged from 7 to 8 out of 9, indicating overall high quality. Five studies[5,11,24,25,35] scored 8, while the other four[10,23,36,37] scored 7. Most studies clearly defined their cases, with diagnoses confirmed by surgical, arthroscopic, or radiological methods. Controls were generally selected from the same populations as the cases and had no history of ACL or related injuries. Some studies did not fully explain how representative their cases were or how controls were selected, which led to slightly lower NOS scores. Most studies accounted for important factors like age, sex, or athletic exposure through their design or analysis. One study[24] had only females in the control group, which might have introduced some bias.

Almost all studies used reliable genotyping methods. In several studies, genotyping was done blind to case/control status, improving reliability. Methods for assessing exposure and outcomes were consistent between cases and controls. Non-response rates were generally low or not reported, but this was not seen as a major concern. Minor limitations included incomplete details on control selection, non-response rates, and blinding in genotyping. Overall, these issues did not affect the high quality of the studies.

Quantitative synthesis

The association between the *rs1800012* and ACL rupture risk was investigated across several genetic models, as illustrated in the forest plots (Figure 2) and summarized in Table 2. In the allele contrast model (T *vs*. G) (Figure 2, A), the pooled Odds Ratio (OR) from the random-effects model was 1.04 (95% CI: 0.90–1.21; $p = 0.61$), suggesting no significant association. Similarly, the dominant model (TT+TG *vs*. GG) (Figure 2, C) showed no significant relationship (OR = 1.15; 95% CI: 0.97–1.37; $p = 0.10$). In contrast, the recessive model (TT *vs*. TG+GG) (Figure 2B) revealed a statistically significant association, indicating that individuals with the TT genotype had a reduced risk of ACL rupture (OR = 0.49; 95% CI: 0.25–0.97; $p = 0.041$). Moreover, the overdominant model (TG *vs*. TT+GG) (Figure 2D) showed a significant association as well, with TG heterozygotes exhibiting a higher risk of ACL rupture (OR = 1.28; 95% CI: 1.07–1.52; $p = 0.006$). Heterogeneity was consistently low across these models, with I^2 values of 0–10%.

Additional genotype comparisons further clarified the genetic contribution of *rs1800012* to ACL rupture risk. The TT vs. GG comparison (Figure 2E) showed a non-significant trend toward a protective effect of the TT genotype (OR = 0.52; 95% CI: 0.25–1.07; $p = 0.074$). A significant association was detected in the TT *vs*. TG comparison (Figure 2F), with the TT genotype linked to a lower risk of ACL rupture (OR = 0.41; 95% CI: 0.21–0.80; $p = 0.009$). Conversely, the TG *vs*. GG comparison (Figure 2G) suggested that individuals with the TG genotype were at greater risk than those with the GG genotype (OR = 1.24; 95% CI: 1.05–1.48; $p = 0.014$). All these findings were derived from random-effects models, and none of the comparisons showed significant heterogeneity (I^2 = 0–15%).

Heterogeneity and subgroup analyses

To explore potential sources of variability in the pooled effect estimates, subgroup analyses were performed based on methodological quality using NOS. The included studies were stratified into two quality tiers: those scoring 8 (n = 5) and those scoring 7 (n = 4). In the allele contrast model (T vs. G), studies with a NOS score of 7 demonstrated a pooled OR of 1.06 (95% CI: 0.83–1.35; p = 0.62), while

studies with a score of 8 showed an OR of 1.03 (95% CI: 0.85–1.24; $p = 0.79$). In the recessive model (TT vs. TG+GG), the overall pooled OR was 0.51 (95% CI: 0.27–0.96; $p = 0.038$), suggesting a significant protective effect of the TT genotype. Notably, across both NOS-based subgroups, heterogeneity remained consistently low, with I^2 values generally under 10%, as shown in Table 3.

Subgroup analysis based on ethnicity was also considered; however, only two studies involved non-Caucasian populations, one conducted in a Han Chinese cohort [23] and the other in an Indian population.[5] Due to the small number of non-Caucasian studies, subgroup analysis by ethnicity was not performed. Similarly, subgroup analysis by gender was deemed infeasible because the majority of included studies did not report genotype distributions separately for males and females. Meta-regression and prediction intervals were not employed in this analysis, as the low heterogeneity observed across all genetic models (I^2 ranging from 0% to 15%) and the stability of the pooled effect estimates across quality subgroups suggested minimal between-study variability.

Sensitivity analyses

Sensitivity analyses were conducted using leave-one-out methods under random-effects models to evaluate the robustness of pooled odds ratios across all genetic models (Figure 3). While the direction and magnitude of association estimates remained consistent in all models, statistical significance in the recessive model (TT vs. TG+GG) was sensitive to the inclusion of certain studies. For example, omitting Stepien-Slodkowska *et al.*[25] resulted in a borderline non-significant effect (OR = 0.45; 95% CI: 0.20–1.01), whereas the pooled estimate remained statistically significant when other studies were excluded. Despite this sensitivity, the overall effect direction remained unchanged, indicating that no single study disproportionately influenced the pooled estimates.

Assessment of publication bias

Publication bias was evaluated for each genetic model using both visual inspection of funnel plots (Figure 4) and Egger's regression test. The funnel plots appeared largely symmetrical for all models, with no obvious evidence of small-study effects. Results of Egger's test further supported the absence of publication bias, with *p*-values as follows: allele contrast (T *vs*. G), $p = 0.9985$; recessive model (TT *vs*. TG+GG), $p = 0.1725$; dominant model, $p = 0.924$; overdominant model, $p = 0.6803$; TT *vs*. GG, $p =$

0.1612; TT *vs*. TG, $p = 0.2693$; and TG *vs*. GG, p = 0.7865. All p-values exceeded the conventional threshold for statistical significance ($p< 0.05$), indicating no significant evidence of publication bias in any model.

Discussion

ACL injury is a multifaceted pathological condition substantially influenced by heredity. Several studies indicate that approximately 70% intraindividual differences in ACL injury susceptibility are attributed to an individual's genetic makeup.[8] Our data demonstrate that TT genotype under recessive model significantly reduces the risk of ACL rupture by 51%, suggesting a protective role of this genotype. Additionally, these findings are supported by other genetic models. For instance, TT *vs*. TG and TT *vs*. GG comparisons were shown to decrease the risk by 59% and 48%, respectively. These findings are consistent with previous studies, which reported a protective role of TT genotype. Wang *et al.*[28] Conducted a meta-analysis pooling six case-control studies and including 933 ACL and other ligament and tendon injury cases and 1,381 controls. Their data indicate a protective role of TT homozygosity. Specifically, in their overall analysis of tendon and ligament injuries, the TT genotype conferred an 80–83% reduction in injury risk compared to other genotypes (OR = 0.17 for TT *vs*. GG and OR = 0.21 for TT *vs*. GT+GG). They concluded that the rare TT genotype provides considerable protection against sports-related connective tissue injuries. Recently, a large meta-analysis study pooled data from 16 studies covering a wide range of musculoskeletal soft tissue injuries (including ACL rupture), reported a protective role of homozygous TT against different musculoskeletal soft tissue injuries. By comparing TT *vs*. GG and TT *vs*. TG, the risk was significantly reduced by half. Nevertheless, this association was most obvious in Caucasian populations, whereas no significant association was found among Asians. Conversely, this was not applicable in our meta-analysis due to the limited number of studies in non-Caucasian ethnicities.[27] Our work is the first to focus exclusively on ACL, prior reviews often pooled heterogeneous injury types, which can dilute ACL-specific association

Our findings show a lack of association under the allele contrast (T *vs*. G: OR = 1.04, 95% CI 0.87–1.24, p = 0.61) and the dominant model (TT+TG *vs*. GG: OR = 1.15, 95% CI 0.93–1.43, p = 0.1). These results are consistent with all individual studies included in our meta-analysis, which also reported no significant association under the allele contrast and dominant models. Similarly, Wang *et*

al.[28] also reported a non-significant association in the allele model (T *vs*. G: OR = 0.89, 95% CI 0.75–1.05, $p = 0.17$) or the dominant model (TT+GT *vs*. GG: OR = 1.00, 95% CI 0.83–1.22, $p = 0.97$). Consistently, Guo *et al.*[27] reported null results for both the allele (T *vs*. G: OR = 0.98, 95% CI 0.86–1.12, $p = 0.79$) and dominant (TT+TG *vs*. GG: OR = 1.05, 95% CI 0.90–1.22, $p = 0.53$) models in their pooled analysis of musculoskeletal soft tissue injuries. This emphasizes that the protective effect of the *rs1800012* variant is limited to the TT genotype and is not present in the presence of a single T allele or dominant inheritance models.

Our results reported that *rs1800012* increases the risk of ACL injuries under an overdominant genetic model, with individuals harboring the heterozygous genotype having a 28% higher odds of ACL rupture compared to both homozygous genotypes (TG *vs*. TT+GG: OR = 1.28, 95% CI 1.07–1.52, $p = 0.006$). These findings are also supported by the TG *vs*. GG comparison, where the TG genotype was associated with a 24% increased risk of ACL rupture relative to the GG genotype (TG *vs*. GG: OR = 1.24, 95% CI 1.05–1.48, p = 0.014). Constantly, Guo et al.[27] found a similar effect specifically in their ACL subgroup analysis, where the TG genotype conferred a 25% higher risk of ACL rupture compared to GG (TG *vs*. GG: OR = 1.25, 95% CI 1.02–1.55, p = 0.03). Support for this overdominant effect and possible heterozygote disadvantage is further observed in several individual studies included in our meta-analysis. For example, Stepień-Słodkowska *et al.*[25] reported that the frequency of the TG genotype was higher among ACL rupture cases (33%) than controls (21%). Similarly, both Khoschnau *et al.*[24] and Posthumus *et al.*[36] observed that heterozygotes had approximately the same odds of ACL injury as GG homozygotes, with the TT genotype being underrepresented among cases and associated with protection. Across these studies, the risk genotype was frequently the heterozygous TG, whereas the TT genotype was under-represented in injury cases, and GG typically served as the baseline group. To the best of our knowledge, this may be attributed to heterozygote disadvantage.

The protective role of *COL1A1* variants against ACL rupture is supported not only for the *rs1800012* polymorphism but also for other functional variants within *COL1A1*. Recently, a meta-analysis of 19 studies was conducted to explore the association between another *COL1A1* variant in the promoter region (*rs1107946*, –1997 G/T). Their data found that the G allele was significantly associated with reduced ACL rupture risk (allele-based OR: 0.27, 95% CI: 0.42 to 0.12, $p < 0.001$). This protective association persisted in the dominant genetic model, where carriers of the G allele had a lower risk of ACL injury (OR: 0.20, 95% CI: 0.38 to 0.01, $p = 0.034$). These findings suggest that the genetic factor for ACL rupture susceptibility may involve different *COL1A1* variants, each potentially acting via

distinct regulatory or structural mechanisms.[38] Furthermore, recent evidence indicates that ACL rupture is influenced not only by variants in *COL1A1* but also by polymorphisms in other genes, including *COL1A2*. For example, a case-control study demonstrated that certain *COL1A2* SNPs (*rs42524* and *rs2621215*) are associated with increased risk of non-contact ACL injury. Notably, their combined analysis revealed that the presence of specific *COL1A1* and *COL1A2* genotypes can produce a cumulative effect on ACL rupture susceptibility, suggesting a potential gene-gene interaction. This emphasizes the significance of considering the combined genetic landscape, rather than single variants alone, when investigating ACL rupture genetic epidemiology. Thus, future genetic association studies should aim to assess multiple polymorphisms and their interplay, which could provide a more comprehensive understanding of the genetic architecture underlying ACL rupture risk.[2]

Ligament is predominantly composed of collagen type I; thus, a slight alteration in the micro-architecture or gene expression of collagen I might impact the biomechanical nature of ACL and increase the vulnerability of rupture. It is documented that the heterozygous genotype of *rs1800012* upregulates *COL1A1* gene expression 3 times compared to wild-type homozygous genotype in human osteoblasts. This imbalance in gene expression yields a higher α1(I) collagen chain output, disturbing the normal 2:1 ratio of α1 to α2 chains. As a result, collagen fibrils can incorporate an excess of α1 chains, leading to formation of homotrimers rather than normal heterotrimers. Indeed, a heterozygous genotype has been reported to alter bone biomechanical strength.[39] These findings offer a compelling explanation for the overdominance pattern observed in ACL injury data. G/T heterozygotes may produce collagens with suboptimal cross-linking or fibril architecture, making ligaments more prone to rupture under stress. These findings offer a plausible explanation for the overdominance pattern observed in ACL injury data. Individuals harboring GT genotype may synthesize collagen with inadequate cross-linking or fibril structure, causing ligaments to be more susceptible to rupture under stress. In contrast, and despite that homozygous TT produces altered collagen composition, TT produces a consistently high α1 output from both alleles, potentially resulting in more uniform collagen fiber. To the best of our knowledge, homotrimer collagen fiber produced by homozygous TT individuals may provide a greater elasticity to ACL. In ligaments, a minor increase in flexibility could potentially reduce the likelihood of an acute tear.[40] While this hypothesis needs to be explored via a direct in vivo study, it offers a rationale for why the TT genotype appears protective and why GT can be detrimental.

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Although genetic factors play a significant role in ACL injury susceptibility, the mechanism of injury represents an indispensable factor in ACL etiology. ACL injuries arise from diverse biomechanical scenarios, primarily non-contact mechanisms like abrupt deceleration, or landing from jumps, as well as from direct or indirect contact trauma and sport-specific injury patterns, such as the skiing-related "phantom foot" falls.[41] Recently, a genetic association study reported a mechanism-specific association between *adiponectin +276G/T* polymorphism and ACL injury exclusively in non-contact sports, highlighting the relevance of injury mechanism in genetic susceptibility.[42] Nevertheless, stratifying cases according to injury mechanism substantially reduces sample sizes, which remains a key limitation in genetic association studies of ACL injury.[43]

The involvement of heredity in complex traits like ACL can vary depending on ethnicity or other environmental factors. The protective TT genotype is rare in most populations, especially among non-Caucasian ethnic groups. Thus, making the detection of T allele requires sufficient sample sizes.[25] Guo *et al*.[27] reported a significant association between TT genotype and musculoskeletal soft tissue injuries in Caucasians, while failing to report an association in Asians. The low allele frequency might explain this in Asian ethnic group. Further studies from diverse ethnic groups would assist in clarifying whether the TT advantage is universally present or mainly a Caucasian phenomenon. This issue is well illustrated by Zhao *et al*.,[23] which examined this association in a Han Chinese population. They reported an extremely low T allele frequency (~1%), consistent with other Asian cohorts. Notably, the low frequency of the T allele in their study led to instability in genotype counts and resulted in deviation from HWE in the control group. This type of deviation is a common and expected phenomenon when the minor allele is rare and sample sizes are modest, and does not necessarily reflect methodological flaws or genotyping errors.[44] These findings necessitate a larger cohort when investigating this association, especially in Asian ethnicity.

A comprehensive understanding of ACL genetic epidemiology will enormously assist in personalized injury prevention strategies. For example, a pilot study genotyped 14 athletes for 124 SNPs related to numerous pathological phenotypes, including ACL rupture. Each individual then received individualized training and preventive recommendations tailored to their genetic risk profile. Their findings demonstrate that participants could adapt a training program based on their identified genetic profile, with follow-up surveys demonstrating changes in behavior after receiving their genetic risk feedback.[45] Nevertheless, recent critical evaluations have emphasized that the current scientific evidence remains insufficient to support the use of genetic polymorphisms for predicting

musculoskeletal injury risk in commercial or clinical settings. In particular, a recent systematic review concluded that commonly tested variants, including *rs1800012*, lack adequate validation, population-wide applicability, and predictive sensitivity to justify their inclusion in direct-to-consumer genetic injury tests. Consequently, while genetic research offers promising insights into ACL injury susceptibility, its translation into applied injury-prevention tools remains premature, and robust prospective studies integrating genetic, biomechanical, and environmental factors are required before widespread implementation.[46,47]

Conclusions

This meta-analysis demonstrates that *rs1800012* TT genotype reduces the risk of ACL rupture by 51% under the recessive model, while the TG genotype increases risk by 28% under the overdominant model. No association was observed for the allele or dominant models. These results clarify genotype-specific effects and highlight the need for further large-scale, multi-ethnic studies before clinical application in risk screening or prevention strategies.

List of Abbreviations

ACL, Anterior Cruciate Ligament

MRI, Magnetic Resonance Imaging

SNP, Single Nucleotide Polymorphism

HWE, Hardy–Weinberg Equilibrium

RFLP, Restriction Fragment Length Polymorphism

PCR, Polymerase Chain Reaction

NOS, Newcastle–Ottawa Scale

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Contributions

Conceptualization, Abdulrahman Bani Kahled and Abdelrahim Alqudah; methodology, Esra Barodi; software, Sajeda Darajah; validation, Mohammed Oqlat, and Eman Shamekh; formal analysis, Mohammad Jawarneh; investigation, Esra Barodi; resources, Abdulrahman Bani Kahled; data curation, Mohammed Oqlat; writing—original draft preparation, Abdulrahman Bani Kahled; writing—review and editing, Mohammad Jawarneh; visualization, Sajeda Darajah; supervision, Abdelrahim Alqudah; project administration, Abdelrahim Alqudah.

Conflict of interest

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Consent for publication

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***SP1* (*rs1800012*) in anterior cruciate ligament injuries**

Table 1. Study quality ratings using the NOS score. The table summarizes how well each study met key quality criteria, with higher star totals indicating stronger overall study design.

Study	Adequate Definition of Cases	Representativeness of Cases	Selection of Controls	Definition of Controls	Comparability*	Exposure Ascertainment	Same Ascertainment Method	Non-response Rate	Total Stars
Stepien-Slodkowska et al. 2017	★	★	★	★	★	★	★	★	8
Khoschnau et al. 2008	★	★	★	★	★	★	★	★	8
Posthumus et al. 2009	★	★	★		★	★	★	★	7
Shukla et al. 2020	★	★	★		★★	★	★	★	8
Sivertsen et al. 2019	★	★	★		★★	★	★	★	8
Massidda et al. 2023	★	★	★		★	★	★	★	7
Zhao et al. 2020	★	★	★		★	★	★	★	7

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Ficek et al. 2013	★	★	★	★★	★	★	★	8
Gibbon et al. 2020	★	★	★	★	★	★	★	7

Table 2. Summary of meta-analysis results for the association between *rs1800012* polymorphism and ACL rupture risk under various genetic models, including odds ratios (OR), confidence intervals (CI), heterogeneity statistics, and type of association

Model	**OR (95% CI)**	**p-value**	**I^2 (%)**	**Heterogeneity p-value**	**Type of Association**
T vs. G (Allele Contrast)	1.04 [0.90–1.21]	0.61	0	0.66	None
TT vs. TG+GG (Recessive)	0.49 [0.25–0.97]	0.041	10	0.36*	Protective
TT+TG vs. GG (Dominant)	1.15 [0.97–1.37]	0.10	0	0.78	None
TG vs. TT+GG (Overdominant)	1.28 [1.07–1.52]	0.006	0	0.91*	Increased Risk
TT vs. GG	0.52 [0.25–1.07]	0.074	15	0.31	Suggestive Protective
TT vs. TG	0.41 [0.21–0.80]	0.009	0	0.43*	Protective
TG vs. GG	1.24 [1.05–1.48]	0.014	0	0.88*	Increased Risk

(*) indicates a significant p-value

***SP1* (*rs1800012*) in anterior cruciate ligament injuries**

Table 3. Summary of findings across genetic models, showing odds ratios, study counts, and statistical significance.

Genetic Model	NOS Score	No. of Studies	OR (95% CI)	p-value	I^2 (%)
Allele Contrast (T vs. G)	7	4	1.06 [0.83–1.35]	0.62	0
	8	5	1.03 [0.85–1.24]	0.79	10.6
Recessive (TT vs. TG+GG)	Overall	8	0.51 [0.27–0.96]	0.038	9.5

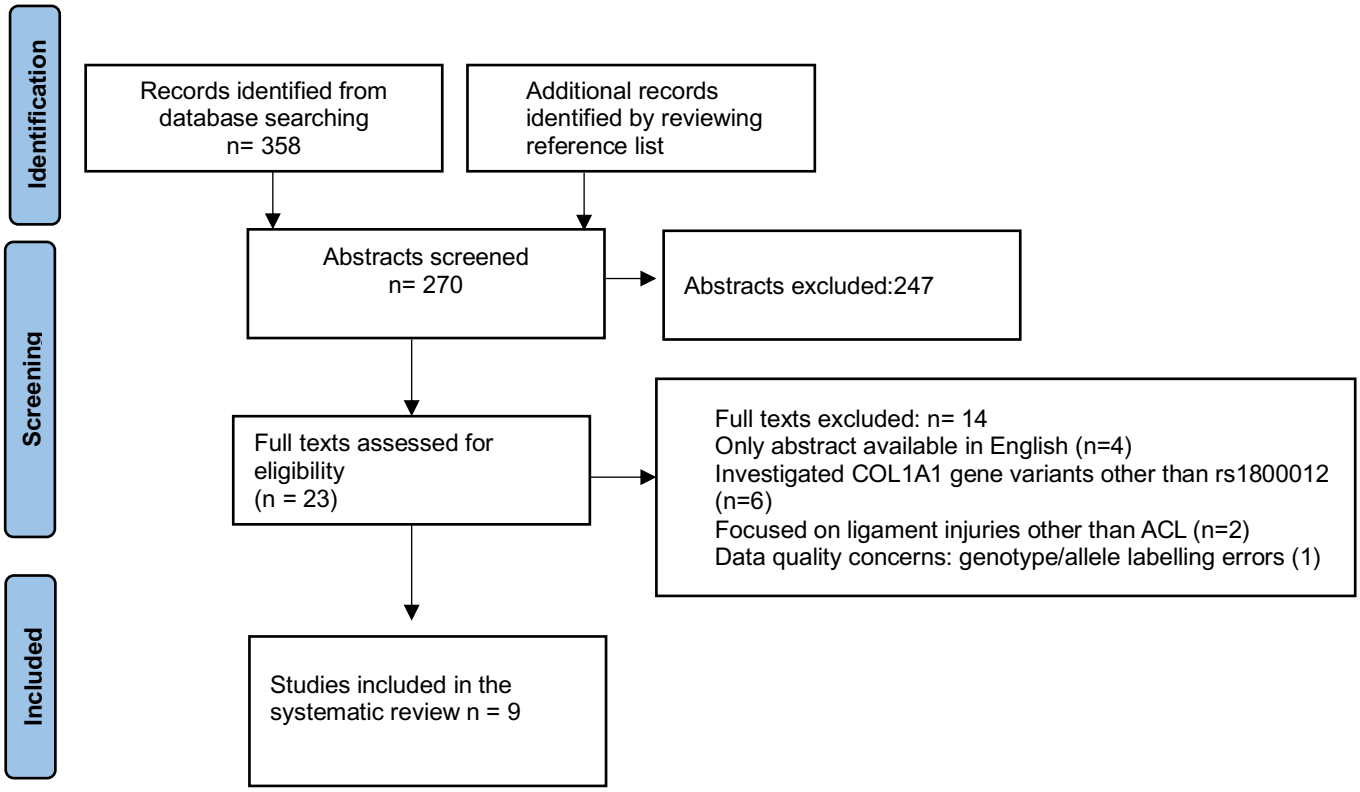

Figure 1. PRISMA Flow Diagram of Study Identification, Screening, and Inclusion for ACL Rupture and Collagen Gene Variant Meta-Analysis.

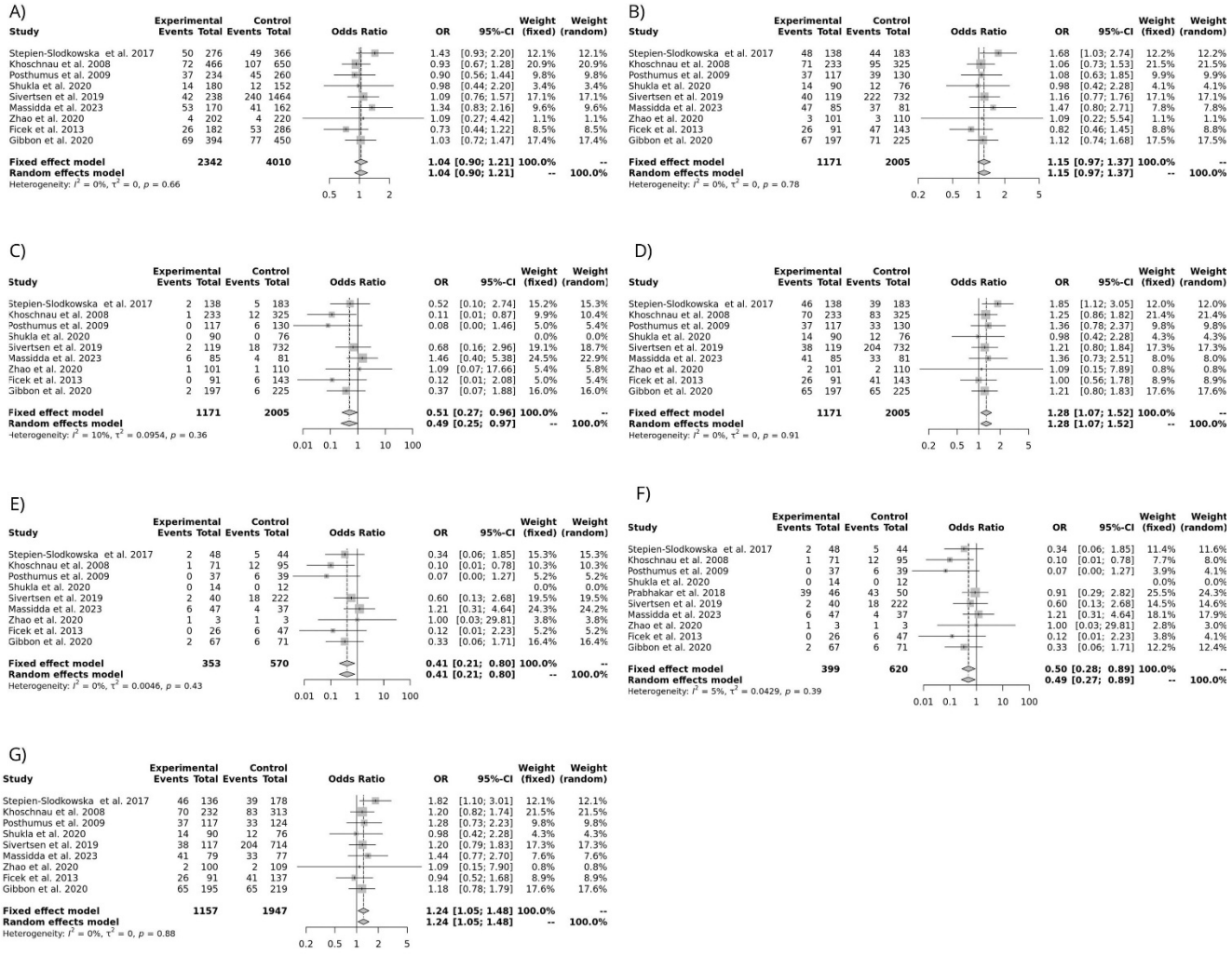

Figure 2. Forest plots of the association between *rs1800012* and ACL rupture risk under different genetic models: A. Allele contrast (T vs. G); B. Recessive model (TT vs. TG+GG); C. Dominant model (TT+TG vs. GG); D. Overdominant model (TG vs. TT+GG); E. TT vs. GG; F. TT vs. TG; G. TG vs. GG.

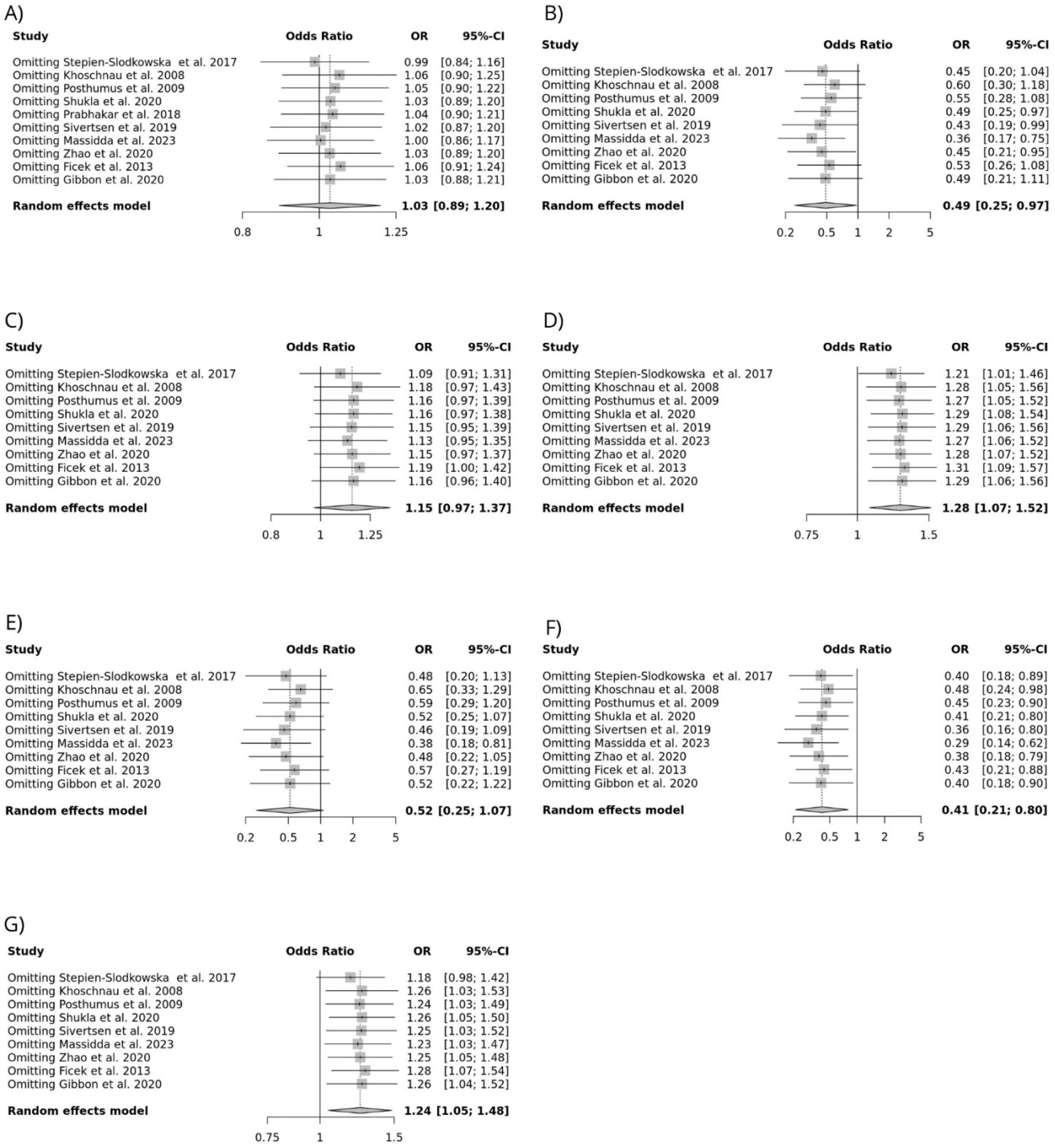

Figure 3. Leave-one-out sensitivity analyses for each genetic model assessing the association between *rs1800012* polymorphism and ACL rupture risk. Odds ratios (OR) and 95% confidence intervals (CI) are shown for each analysis, with each study omitted in turn. Genetic models: A. Allele contrast (T vs. G); B. Recessive model (TT vs. TG+GG); C. Dominant model (TT+TG vs. GG); D. Overdominant model (TG vs. TT+GG); E. TT vs. GG; F. TT vs. TG; G. TG vs. GG.

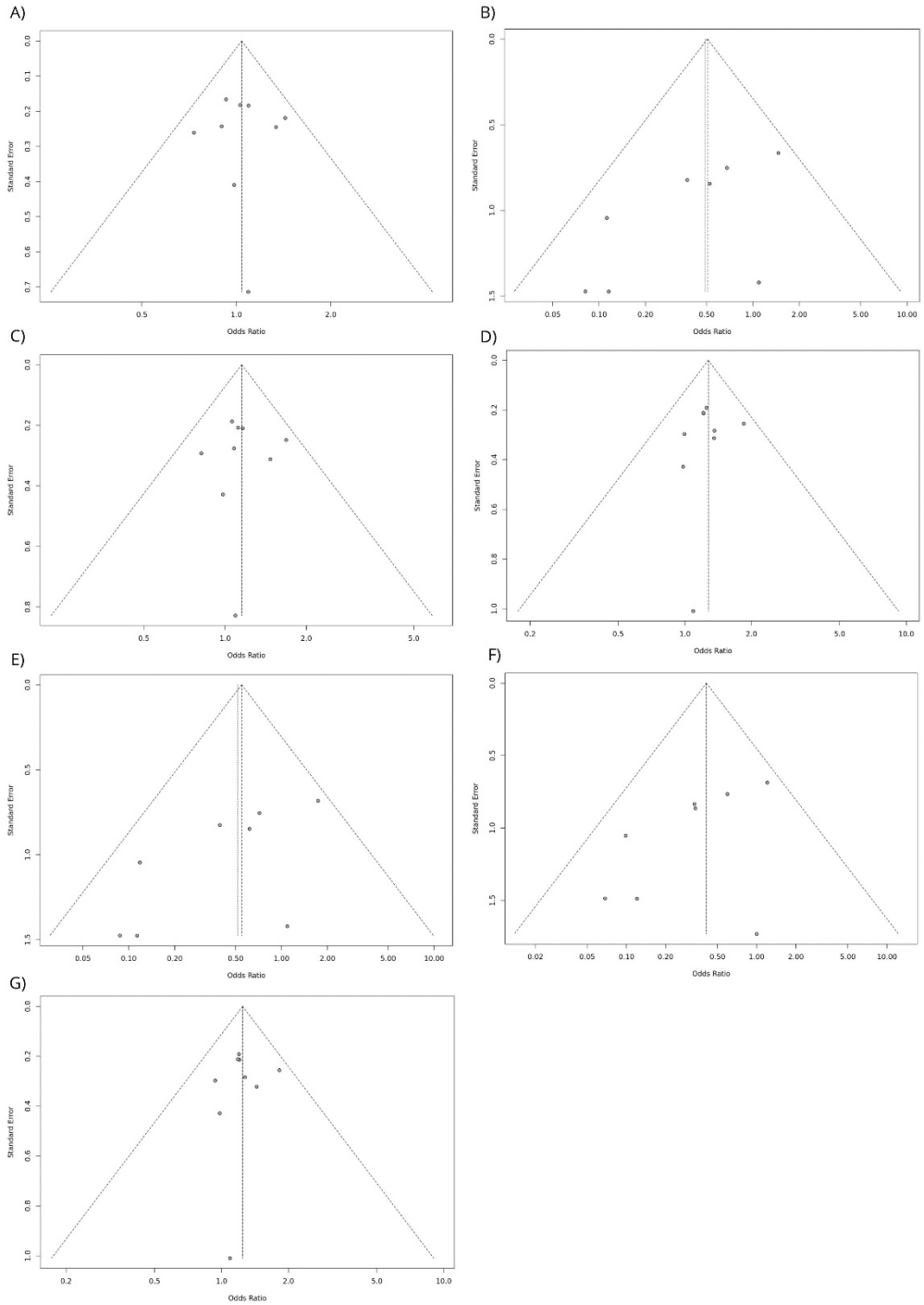

Figure 4. Funnel plots for assessment of publication bias in each genetic model (A–G) for the association between *rs1800012* polymorphism and ACL rupture risk. Each dot represents an individual study; the dashed lines represent the expected 95% confidence limits in the absence of publication bias. Genetic models: A. Allele contrast (T vs. G); B. Recessive model (TT vs. TG+GG); C. Dominant model (TT+TG vs. GG); D. Overdominant model (TG vs. TT+GG); E. TT vs. GG; F. TT vs. TG; G. TG vs. GG

Online supplementary materials

Table 1. Genotype Distributions, Allele Frequencies, and Study Characteristics for rs1800012 in ACL Injury Cases and Controls.