Association of aspartic acid repeat polymorphism in the asporin gene with osteoarthritis of knee, hip, and hand
A PRISMA-compliant meta-analysis

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Abstract

Objective: Several human studies have been conducted to explore the association between asparin (ASPN) D-repeat polymorphisms and OA susceptibility, but these provide inconsistent results. Our primary aim is to examine whether D-repeat polymorphisms are related to OA risk.

Methods: We conducted a meta-analysis to investigate the association between ASPN D-repeat polymorphisms and OA. Electronic database was searched, including PubMed, Embase, CNKI, Ovid, and the reference lists of relevant articles published from the inception to January 24, 2018. The included studies were assessed in the following allele model: D14 allele versus others combined, D13 allele versus others combined, D15 allele versus others combined, and D14 allele versus D13 allele. Female population was also analyzed separately.

Results: Eleven articles (12 comparisons) with 4975 patients of knee, hip, and/or hand OA and 3754 controls were considered in this meta-analysis. For the D13 allele, OR and 95% CI in combined population indicated an borderline association (odds ratio [OR] = 0.94, confidence interval [CI]: 0.89–0.99, \( P = .027 \)). No significant association between OA and the D14 allele and D15 allele in all pooled studies were observed.

Conclusion: Our result based on previously published studies demonstrated that the ASPN D13 allele was a protective factor for OA of knee, hip, and hand. For D14 and D15 allele, our present meta-analysis did not demonstrate statistically significant association. Further studies with larger sample size would be required.

Abbreviations: ASPN = asporin, D-repeat = aspartic acid residues, ECM = extracellular matrix, GWAS = genome-wide association studies, NOS = Newcastle-Ottawa Scale, OA = osteoarthritis, SLRPs = small leucine-rich proteoglycans, TGF-\( \beta \) = transforming growth factor-\( \beta \).

Keywords: asporin, meta-analysis, osteoarthritis, polymorphism

1. Introduction

As the most common form of arthritis in humans, osteoarthritis (OA) is a chronic condition characterized by the progressive loss of articular cartilage in synovial joints and regarded as a disease of the entire joint.\textsuperscript{[1]} Symptoms of OA include joint pain and stiffness, which can eventually lead to disability. Compelling evidence have suggested that OA is associated with substantial economic burden and overwhelmingly serious socioeconomic consequences.\textsuperscript{[2]} OA has emerged as one of the major public health concerns and continues to affect about 10% of men and 18% of women over 60 years of age worldwide.\textsuperscript{[1,1\textsuperscript{1}]} The etiology of OA is multifactorial with a clear genetic component. Twins and other family-based studies have assessed the estimated heritability for OA in the range of 40% to 63% depending on the joint site.\textsuperscript{[1\textsuperscript{1}]} The genetic background of OA likely involves multiple genes that encode proteins with significant functions in the underlying disease process, suggesting that genetic factors are strong determinants of OA development.\textsuperscript{[3]} It is demonstrated that small leucine-rich proteoglycans (SLRPs), a group of biologically active components of the extracellular matrix (ECM) of many tissues, have been essential in regulating cell biology, differentiation, and migration behavior of mesenchymal stem cell-derived progenitor cells, which play an important part in the chronic and inflammation-related OA pathogenesis.\textsuperscript{[3–7]}

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Like many other SLRPs, asporin (ASPN), a class I SLRP, is a protein of ECM. ASPN binds transforming growth factor-β (TGF-β) which is a key growth factor in cartilage metabolism, and the evidence in vitro shows that ASPN acts as negative regulator of chondrogenesis by inhibiting TGF-β function.\[8\] Besides, evidence have suggested the expression of ASPN in cartilage of individuals with OA is greater than that of unaffected adults.\[9,10\]

The gene that encodes ASPN protein located on human chromosome 9q22-9q21.3, possessing a unique stretch of aspartic acid residues (D-repeat) in its N-terminal region.\[11,12\] The number of D-repeats differs from D 9 allele to D 20 allele, and each variant of D-repeats might play a different part in OA pathogenesis because D-repeats might influence asporin, just as the D-repeat in osteoarthritis acts as a Ca\(^{2+}\)-binding domain and affects its function.\[4,13\] A number of population studies have been conducted to explore the association between D-repeat polymorphisms and OA susceptibility, but these provide inconsistent results.\[14-24\] D13 was found to be a protective factor against OA in Japanese,\[14,19\] while D14 was reported to be a risk factor of knee OA development in Chinese Han populations.\[18,23\] Additionally, D15 might be a risk factor for OA in women.\[12,21\] Nevertheless, similar positive association was not detected in United States or Mexico.\[19,24\]

Recently, 3 meta-analyses based on different strategies have suggested the possible association of ASPN D-repeat polymorphisms with OA development.\[26-28\] However, previous meta-analysis specifically focused on D14 and D13 allele only for knee OA.\[26,27\] In addition, a meta-analysis published in 2014 with 9 studies was conducted to explore the association between ASPN and OA of the knee and hip sites among each ethnic group. However, the combined data in Latin American population remains vacant.\[28\] Several new studies on the D-repeat polymorphisms with OA have been reported successively.\[23,24\] Therefore, an updated study needs to be conducted. More to the point, more reliable estimates of ASPN D-repeat polymorphisms with different OA sites are warranted such as knee, hip, and hand sites. In our study, a relatively comprehensive meta-analysis was performed to explore whether ASPN D-repeat polymorphism is associated with OA susceptibility stratified by OA site and ethnicity.

2. Methods

2.1. Search strategy

We systematically searched electronic database including PubMed, Embase, CNKI, and Ovid based on logic combination of keywords and text words to identify available articles from the inception to January 24, 2018. The Internet-based search strategy used the following terms: “arthritis,” “osteoarthritis,” “OA,” “joint disease,” “aspirin,” “ASPN,” “D-repeat,” “aspartic acid,” “polymorphism,” “polymorphisms,” and the corresponding free terms. The search was limited to studies of population, and no language or country restriction was placed. We then screened reference lists of all obtained articles, including relevant reviews, to avoid missing relevant articles.

2.2. Inclusion and exclusion criteria

Studies in this meta-analysis must meet the following inclusion criteria: observational studies that addressed OA patients and healthy controls, diagnosed OA based on clinical and radiographic findings and/or ascertained by total joint replacement, original studies that provided genotype or allele data for extraction to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). Exclusion criteria: comment and review, duplication of previous publication, family-based studies of pedigrees, study with no detailed genotype data.

2.3. Data extraction

Two investigators (XYZ and YHL) independently assessed all studies for eligibility and extracted data in accordance with a preconfigured form from each study. Any disagreements were resolved through discussion with a third reviewer (LYJ). The following contents were collected: name of first author, year of publication, ethnicity, demographics, joint affected, the sample size of case and control, and allele frequencies.

2.4. Quality assessment

The quality of the included studies was assessed by 2 authors respectively according to the Newcastle-Ottawa Scale (NOS) (Supplemental Digital Content 1, http://links.lww.com/MD/C173). In the scale, 3 critical aspects, including the selection, comparability, exposure, were carefully scrutinized. Two investigators scored the studies independently and the discrepancies between the reviewers were resolved by reaching consensus.

2.5. Statistics analysis

We conducted our meta-analysis to determine the association of ASPN D14 allele and D13 allele with OA. The included studies are based on following allele model: D14 allele versus others alleles combined, D13 allele versus others allele combined, and D14 allele versus D13 allele. Besides, we performed a profound analysis allowing for D15 allele with OA. OR and 95% CIs were calculated to evaluate the strength of the association between these potential D14 allele or D13 alleles and susceptibility to OA.

The heterogeneity between studies was tested using the Q statistics, \(P < .1\) was considered statistically significant. And, \(I^2\) was used to quantify the inconsistency among the potentially disparate sources of studies. Either fixed-effect model or random effect model was employed to pool the effect size according to the heterogeneity. A sensitivity analysis was performed to evaluate the effect of each study on the combined ORs by omitting each study.

Publication bias was then checked by Begg funnel plots and Egger regression test, which measure the degree of funnel plot asymmetry. STATA (version 13.1, StataCorp, College Station, TX) were used for all analyses.

3. Results

3.1. Study selection and characteristics

The summary of study search and selection was presented in Fig. 1. Among the 105 records identified through literature search, 14 articles were selected for a full-text review. However, 2 articles were excluded because they only reported the ASPN rs13001537 and the association with OA.\[29,30\] One article was duplicated from a previous study reported in the year 2006.\[18,23\] In addition, 1 paper covered the data of 2 different studies.\[14\] Thus, 11 articles (12 separate studies) were employed to assess the ASPN D-repeat polymorphisms and susceptibility to
Meanwhile, only 6 studies conducted stratification according to sex of participants. So we also evaluated the possible association of ASPN D-repeat polymorphisms with OA in the female population.\textsuperscript{[15,17,18,20,22,23]}

In total, 12 comparisons with 4975 patients of knee, hip, and/or hand OA and 3754 controls were considered in this meta-analysis, which involved 5 papers from Asian, 4 Caucasian, and 3 Latin American. Eleven articles were examined for the D14 and D13 alleles, and all 10 articles were scrutinized for the D15 alleles. Twelve studies reported knee OA, 3 studies examined hip OA, and 1 study provided data of hand OA, respectively. Among these 12 separate studies, 1 was cohort study and others were case-controlled designs. Characteristics of the ASPN polymorphism studies were presented in Table 1.

Table 2 showed allele counts for D-repeat polymorphism in ASPN and the frequency of the D13 and D14 allele in Asian, Caucasian, and Latin American population. We evaluated D13 and D14 allelic frequency respectively and the difference of allele frequency among the 3 ethnic groups were statistically significant ($\chi^2 = 337.02, P < .001$). Additionally, alleles of D14, D13, and D15 for women were also counted respectively and 6 comparisons with 1793 female OA patients and 1152 female controls were analyzed (Supplemental Digital Content 2, http://links.lww.com/MD/C173).

### 3.2. Association between d-repeat polymorphism and OA susceptibility

Twelve studies that evaluated the association between D-repeat polymorphism and susceptibility to OA were identified (Table 3). The summary OR for the D13 allele versus other alleles combined and its 95\% CI indicated that D13 allele was found to be associated with OA (OR = 0.94, 95\% CI: 0.89–0.99, $P = .027$). In the subgroup analysis based on ethnicity, no significant association between the D13 allele and OA in all pooled studies was observed (Table 3; Fig. 2). After stratification by joint affected, there was no association between D13 allele and knee OA.\textsuperscript{[14–24]}

![Figure 1. The summary of study search and selection.](http://links.lww.com/MD/C173)
and/or hip OA in the Asian, Caucasian, and Latin American population (Table 3; Fig. 2).

No significant association between the D14 allele and OA in all pooled studies was observed (OR = 1.13, 95% CI: 0.98–1.31, P = .102). After being stratified by ethnicity, there was no association between D14 allele and OA among the Asian, Caucasian, and Latin American populations (Table 3; Fig. 3). Stratification by joint affected showed no association between the D14 allele and knee or hip OA in all study subjects (Table 3).

There was no significant difference between D14 and D13 allele in the development of OA in all races combined. Furthermore, stratification by ethnicity failed to identify the association in the 3 population. Stratification by joint affected also revealed no association between the D-repeat polymorphism and susceptibility to knee OA and hip OA in the Asians, Caucasians, and Latin Americans (Table 3; Supplemental Digital Content 3, http://links.lww.com/MD/C173). Moreover, no association was found between the ASPN D15 allele and OA risk (OR = 1.01, 95% CI: 0.93–1.10, P = .448). For ASPN D15 allele, stratification by ethnicity or joint affected was also unable to identify this association (Supplemental Digital Content 4, http://links.lww.com/MD/C173). In addition, when stratified by sex, the association between D-repeat polymorphism and susceptibility to OA was not observed in the female population (Supplemental Digital Content 5, http://links.lww.com/MD/C173).

### 3.3. Heterogeneity and publication bias

The between-study heterogeneity in terms of the ORs of the D14 and D13 polymorphism was detected in several subjects. If I² was >50%, random effect model was used. Otherwise, fixed effect model was applied (Table 3; Figs. 2 and 3). No publication bias was found for the association between D14 allele and OA susceptibility, which was identified by Begg funnel plot (P = .837) or Egger regression test (P = .490) (Supplemental Digital Content 6, http://links.lww.com/MD/C173). And, no publication bias was observed in the meta-analysis of the D13 allele versus others (Egger test P = .871), D15 alleles versus others (Egger test P = .650), and D14 versus D13 alleles (Egger test P = .605).

### Table 1

Characteristics of the included studies.

| First author | Year | Country | Ethnicity | Study design | Eligible subjects (n) | Age (y) | Joint affected |
|--------------|------|---------|-----------|--------------|-----------------------|---------|---------------|
| Kizawa       | 2005 | Japan   | Asian     | Cohort       | 137 234               | NA NA   | Knee          |
| Kizawa       | 2005 | Japan   | Asian     | Case-control | 986 374               | NA NA   | Knee, hip     |
| Mustafar     | 2005 | UK      | Caucasian | Case-control | 1247 748              | >55     | Knee, hip, hand |
| Kakakatos    | 2006 | Greece  | Caucasian | Case-control | 158 193               | 68.60   | Knee          |
| Rodriguez-Lopez | 2006 | Spain   | Caucasian | Case-control | 723 294               | 58.10   | Knee, hand    |
| Jiang        | 2006 | China   | Asian     | Case-control | 218 454               | 68.20   | Knee          |
| Atif         | 2008 | USA     | Caucasian | Case-control | 775 511               | 58.10   | Knee, Hand    |
| Song         | 2008 | Korea   | Asian     | Case-control | 190 376               | 60.00   | Knee          |
| Arellano     | 2013 | Mexico  | Latin American | Case-control | 218 222               | 57.99   | Latin American |
| Jazayer      | 2013 | Iran    | Asian     | Case-control | 100 100               | 63.00   | Knee          |
| Arellano     | 2014 | Mexico  | Latin American | Case-control | 130 130               | 59.05   | Knee          |
| Gonzalez-Huerta | 2015 | Mexico  | Latin American | Case-control | 93 118               | 56.40   | Knee          |

n = number, NA = not available, OA = osteoarthritis, y = year.

### Table 2

Allele counts for the D-repeat polymorphism in ASPN in the included studies.

| Group        | Author            | Count | Frequency | Count | Frequency |
|--------------|-------------------|-------|-----------|-------|-----------|
|              |                   | D13   | D14       | D13   | D14       |
| Asian        | Kizawa Cohort     | 163   | 30 81     | 0.59  | 0.11      |
|              | Kizawa Case-control | 1190 | 155 627   | 0.60  | 0.08      |
|              | Jiang             | 300   | 41 95     | 0.69  | 0.09      |
|              | Song              | 265   | 22 93     | 0.70  | 0.06      |
|              | Jazayer           | 82    | 32 86     | 0.41  | 0.16      |
|              |                   | 2000  | 280 982   | 0.61  | 0.09      |
| Caucasian    | Mustafar          | 1183  | 352 959   | 0.47  | 0.14      |
|              | Kakakatos         | 118   | 47 145    | 0.38  | 0.15      |
|              | Rodriguez-Lopez   | 627   | 172 649   | 0.43  | 0.12      |
|              | Atif              | 749   | 206 595   | 0.48  | 0.13      |
|              |                   | 2677  | 777 2348  | 0.46  | 0.13      |
| Latin American | Arellano           | 205   | 91 140    | 0.41  | 0.21      |
|              | Gonzalez-Huerta   | 7     | 123 56    | 0.04  | 0.66      |
|              | Arellano-Perez-Vertti | 85    | 49 78    | 0.40  | 0.23      |
|              |                   | 297   | 263 274   | 0.36  | 0.32      |

x² = 337.02, P < .001

| Group        | Count | Frequency |
|--------------|-------|-----------|
|              | D13   | D14       |
| Asian        | 314   | 22 81     |
|              | 604   | 44 95     |
|              | 483   | 65 93     |
|              | 91    | 40 86     |
|              | 1971  | 207 982   |
| Caucasian    | 752   | 190 959   |
|              | 189   | 53 145    |
|              | 248   | 74 649    |
|              | 436   | 142 595   |
|              | 1685  | 459 2348  |
| Latin American | 204   | 107 140   |
|              | 6     | 134 56    |
|              | 85    | 51 78     |
|              | 295   | 292 274   |

χ² = 485.38, P < .001

ASPN = asporin.
3.4. Sensitivity analysis

Sensitivity analysis was performed to examine the influence set by the individual study on the pooled ORs for ASPN D-repeat polymorphism by deleting each study. After deleting 3 studies of Latin American, the pooled OR still showed the stable association with OA susceptibility for the comparison of D13 allele versus other alleles combined (OR = 0.93, 95% CI: 0.88–0.99, P = .017), which indicated a significant association. When 5 articles about Asian population were removed, the pooled OR showed no statistical significance (OR = 0.94, 95% CI: 0.89–1.01, P = .100). In addition, for D14 allele, high heterogeneity was found in Asian population. After removing the cohort study of Kizawa, the pooled estimate remained no statistically significant in the comparison of D14 allele versus other alleles combined (OR = 1.09, 95% CI: 0.95–1.25, P = .207). Consistently, when omitting each study, no significant association with OA was detected in the comparison of D15 allele versus other alleles combined.

4. Discussion

OA is considered as a complex and multifactorial disorder. The prevalence of OA, particularly of the large weight-bearing joints such as the knee and hip, is also predicted to increase in recent years.[1,31] Currently, therapeutic approaches focus on slowing progression of OA rather than prevention efforts.[4,34] Although the etiology of OA remains unknown, it is believed that OA is a polygenic disease influenced by genetic components and environmental factors.[35,36] In our meta-analysis, 11 eligible case-control studies and 1 cohort study including 4975 cases and 3754 controls were included to explore the association of ASPN D-repeat polymorphism with knee, hip, and hand OA susceptibility in different origin of ethnicities.

Emerging evidence has suggested the involvement of ASPN in OA pathogenesis. Except for its influence on the canonical TGF-β pathway, ASPN could also bind collagen and calcium to induce the biominerallization of collagen.[4] Moreover, direct evidence from several population-based studies showed that D14 could be a risk factor of OA and D13 serving as a protective factor against OA. Meanwhile, D15 allele could be a risk factor of OA especially for women.[14,22,37] However, in this meta-analysis, there was not enough evidence to support the association between the ASPN D14 or D15 alleles and OA susceptibility in different ethnicities and in different joints, which was consist with the result of a previous meta-analysis.[26,28] For the D13 allele, OR, and 95% CI in combined population indicated a borderline association (OR = 0.94, 95% CI: 0.89–0.99, P = .027), which was inconsistent with other meta-analyses.[28] Previous meta-analyses indicated that no association was found between the ASPN D13 allele and OA susceptibility.[28] However, significant association between the D13 allele and the susceptibility to OA of knee, hip, and hand has been demonstrated in the present study.

In this meta-analysis, we further examined the association of ASPN D-repeat polymorphism with OA in female population.
Only 6 included studies reported the allele frequency of women participants. Overall, the pooled results for women demonstrated that no significant correlation was observed between D15 allele and OA susceptibility. Also, similar results of D13 and D14 allele for women were detected. Kaliakatsos et al\[16\] reported D15 could be a risk factor for OA. Moreover, findings from Jazayeri and colleagues suggested D15 allele could be a risk factor for women only.

Compared with previous meta-analysis published in 2014, 2 new articles were included in this study.\[28\] In the subgroup analysis based on ethnicity, studies were divided into Asian, Caucasian, and Latin American populations. Therefore, we could obtain the result of Latin Americans, which was relatively profound and definitely different from previous analysis. Furthermore, stratification according to sex was also conducted in this meta-analysis. Although no significant association was observed for the ASPN D-repeat polymorphism and OA risk, the effect values did exhibit the same trend compared with the present studies in the pathogenesis of OA.\[4,38\]

Although our present analyses indicated an association of ASPN D13 allele with OA and showed no statistical association between D14 and D15 allele in the development of OA, our results should be interpreted with caution with the following reasons. Firstly, heterogeneity could have distorted the meta-analysis. The test of heterogeneity in several types of population was shown to be significant, suggesting potential genetic heterogeneity among different population. Secondly, we were unable to conduct subgroup analysis for confounding factors, such as age and occupation because of original data restraints. And, it was more reasonable to stratify the severity of OA, since patients of 3 studies had undergone joint replacement, which presumably indicate severe OA. Raw data of female was inadequate to detect this association. Thirdly, we were unable to test the interaction between the alleles and environmental risk factors due to absence of such information on environmental risk factors in the original data.

In conclusion, our results based on previously published studies have demonstrated that the ASPN D13 allele was a protective factor for OA of knee, hip, and hand. For D14 and D15 allele, our present study did not demonstrate statistical association. However, there was still lacking sufficient stability to draw an accurate conclusion because of the restricted sample size. Several potential genes of susceptibility to OA have already been reported by many genome-wide association studies (GWAS) which had proved to be successful in identifying genetic association with complex traits. Nevertheless, no available

![Figure 2. Forest plot of ASPN D-repeat polymorphism and OA for the comparison of D13 allele versus other alleles combined. ASPN = asporin, OA = osteoarthritis.](image-url)
studies on ASPN gene with OA development have been reported by these GWAS studies.[3] Well-designed studies with larger sample size and more ethnic groups are further required to validate the risk of ASPN on the onset and progression of disease.

5. Author contributions

Xiaoyue Zhu drafted the protocol and wrote the final paper. Liying Jiang contributed to the research design and made critical revisions. Yihua Lu, Chunli Wang, He Wang participated in the data collection. Shuai Zhou and Tian Tian participated in the data analysis. All authors reviewed the final version of the manuscript and approve it for publication.

References

[1] Glyn-Jones S, Palmer AJR, Agricola R, et al. Osteoarthritis. Lancet 2015;386:376–87.
[2] Valdes AM, Loughlin J, Timms KM, et al. Genome-wide association scan identifies a prostaglandin-endoperoxide synthase 2 variant involved in risk of knee osteoarthritis. Am J Hum Genet 2008;82:1231–40.
[3] arcOGEN Consortium, arcOGEN Collaborators, Zeggini E, et al. Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. Lancet 2012;380:2123–21.
[4] Xu L, Li Z, Liu SY, et al. Asporin and osteoarthritis. Osteoarthritis Cartilage 2015;23:933–9.
[5] Chang HX, Yang L, Li Z, et al. Age-related biological characterization of mesenchymal progenitor cells in human articular cartilage. Orthop Dists 2011;34:e382–8.
[6] Gerster R, Kruegel J, Miosge N. New insights into cartilage repair - the role of migratory progenitor cells in osteoarthritis. Matrix Biol 2012;31:206–13.
[7] Chen XD, Bian X, Teslovich TM, et al. Dissection of the sets of genes that control the behavior of biglycan-deficient pre-osteoblasts using oligonucleotide microarrays. Bone 2005;37:192–203.
[8] Ommerford P, Khalib A, Reinholt FP, et al. Quantitative proteomic analysis of eight cartilaginous tissues reveals characteristic differences as well as similarities between subgroups. J Biol Chem 2012;287:18913–24.
[9] Henry SP, Takanosu M, Boyd TC, et al. Expression pattern and gene characterization of asporin, a newly discovered member of the leucine-rich repeat protein family. J Biol Chem 2001;276:12123–21.
[10] Nakajima M, Kizawa H, Satoh M, et al. Mechanisms for asporin function and regulation in articular cartilage. J Biol Chem 2007;282:32185–92.
[11] Ikegawa S. Expression, regulation and function of asporin, a susceptibility gene in common bone and joint diseases. Curr Med Chem 2008;15:724–8.
[12] Kajikawa T, Yamada S, Tauchi T, et al. Inhibitory effects of PLAP-1/asporin on periodontal ligament cells. J Dent Res 2014;93:400–5.
[13] Singh K, Deonaraine D, Shammugam V, et al. Calcium-binding properties of osteopontin derived from non-osteogenic sources. J Biochem 1993;114:702–7.
[14] Kizawa H, Koi I, Iida A, et al. An aspartic acid repeat polymorphism in asporin inhibits chondrogenesis and increases susceptibility to osteoarthritis. Nat Genet 2005;37:138–44.
Mustafa Z, Dowling B, Chapman K, et al. Investigating the aspartic acid (D) repeat of asporin as a risk factor for osteoarthritis in a UK Caucasian population. Arthritis Rheum 2005;52:3502-6.

Kalialakatsos M, Tzetsis M, Kanavakis E, et al. Asporin and knee osteoarthritis in patients of Greek origin. Osteoarthritis Cartilage 2006;14:609-11.

Rodriguez-Lopez J, Pombo-Suarez M, Liz M, et al. Lack of association of a variable number of aspartic acid residues in the asporin gene with osteoarthritis susceptibility: case-control studies in Spanish Caucasians. Arthritis Res Ther 2006;8:R55.

Jiang Q, Shi D, Yi L, et al. Replication of the association of the aspartic acid repeat polymorphism in the asporin gene with knee-osteoarthritis susceptibility in Han Chinese. J Hum Genet 2006;51:1068-72.

Atif U, Philip A, Aponte J, et al. Absence of association of asporin polymorphisms and osteoarthritis susceptibility in US Caucasians. Osteoarthritis Cartilage 2008;16:1174-7.

Song JH, Lee HS, Kim CJ, et al. Aspartic acid repeat polymorphism of the asporin gene with susceptibility to osteoarthritis of the knee in a Korean population. Knee 2008;15:191-5.

Arellano RD, Hernandez F, Garcia-Sepulveda CA, et al. The D-repeat polymorphism in the ASPN gene and primary knee osteoarthritis in a Mexican mestizo population: a case-control study. J Orthop Sci 2013;18:826-31.

Jazayeri R, Qoreishi M, Hoseinzadeh HR, et al. Investigation of the asporin gene polymorphism as a risk factor for knee osteoarthritis in Iran. Am J Orthop (Belle Mead NJ) 2013;42:313-6.

Arellano-Perez-Vertti RD, Arguello-Astorga JR, Cortez-Lopez ME, et al. D-repeat polymorphism in the ASPN gene in knee osteoarthritis in females in Torreon, Coahuila. Case-control study. Acta Ortop Mex 2014;28:363-8.

Gonzalez-Huerta NC, Borgonio-Cuadra VM, Zenteno JC, et al. D14 repeat polymorphism of the asporin gene is associated with primary osteoarthritis of the knee in a Mexican Mestizo population. Int J Rheum Dis 2017;20:1935-41.

Shao Z, Qin J, Dai J, et al. Association of asporin gene polymorphism and knee osteoarthritis. Chin J Public Health 2008;24:538-9.

Xing D, Ma XL, Ma JX, et al. Association between aspartic acid repeat polymorphism of the asporin gene and susceptibility to knee osteoarthritis: a genetic meta-analysis. Osteoarthritis Cartilage 2013;21:1700-6.

Sobhan MR, Mehdinejad M, Jamaladini MH, et al. Association between aspartic acid repeat polymorphism of the asporin gene and risk of knee osteoarthritis: a systematic review and meta-analysis. Acta Orthop Traumatol Turc 2017;51:409-15.

Song GG, Kim JH, Lee YH. A meta-analysis of the relationship between aspartic acid (D)-repeat polymorphisms in asporin and osteoarthritis susceptibility. Rheumatol Int 2014;34:785-92.

Liang W, Gao B, Xu G, et al. Association between single nucleotide polymorphisms of asporin (ASPN) and BMP5 with the risk of knee osteoarthritis in a Chinese Han population. Cell Biochem Biophys 2014;70:1603-8.

Bijsterbosch J, Kloppenburg M, Reijnierse M, et al. Association study of candidate genes for the progression of hand osteoarthritis. Osteoarthritis Cartilage 2013;21:563-9.

Blagoev M, Jinks C, Jeffer A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010;18:24-33.

Leung GJ, Rainsford KD, Kean WF. Osteoarthritis of the hand I: aetiology and pathogenesis, risk factors, investigation and diagnosis. J Pharma Pharmacol 2014;66:339-46.

Silverwood V, Blagoevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2015;23:307-15.

Spanakis K, Spanakis EG, Kondylakis H, et al. Addressing drug-drug and drug-food interactions through personalized empowerment services for healthcare. Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference. Aug 2016; 5640-5643.

Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med 2010;26:355-69.

Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum Dis Clin North Am 2013;39:1-9.

Poulou M, Kalialakatsos M, Tsezou A, et al. Association of the CALM1 core promoter polymorphism with knee osteoarthritis in patients of Greek origin. Genet Test 2008;12:263-5.

Ni GX, Li Z, Zhou YZ. The role of small leucine-rich proteoglycans in osteoarthritis pathogenesis. Osteoarthritis Cartilage 2014;22:896-903.