Systematic Review and Meta-Analysis

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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 aspirin (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-β = transforming growth factor-β.

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.[1] Symptoms of OA include join 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.[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.[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 65% depending on the joint site.[3]

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.[4] 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.[5–7]

Editor: Giovanni Tarantino.

Disclosure: This study did not warrant institutional review board approval as no human subjects were involved.

This study was supported by the Research Innovation Program for College Graduates of Jiangsu Province (YKC16019).

Competing interests: The authors declare that they have no competing of interests.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:12(e0200)

Received: 23 November 2017 / Received in final form: 25 February 2018 / Accepted: 27 February 2018

http://dx.doi.org/10.1097/MD.0000000000010200

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 aspirin, 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] while D14 was reported to be a risk factor of knee OA development in Chinese Han populations.[18,25] Additionally, D15 might be a risk factor for OA in women.[4,22] 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 enthnicity.

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 rs 13001537 and the association with OA.[29,30] One article was duplicated from a previous study reported in the year 2006.[18,25] 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

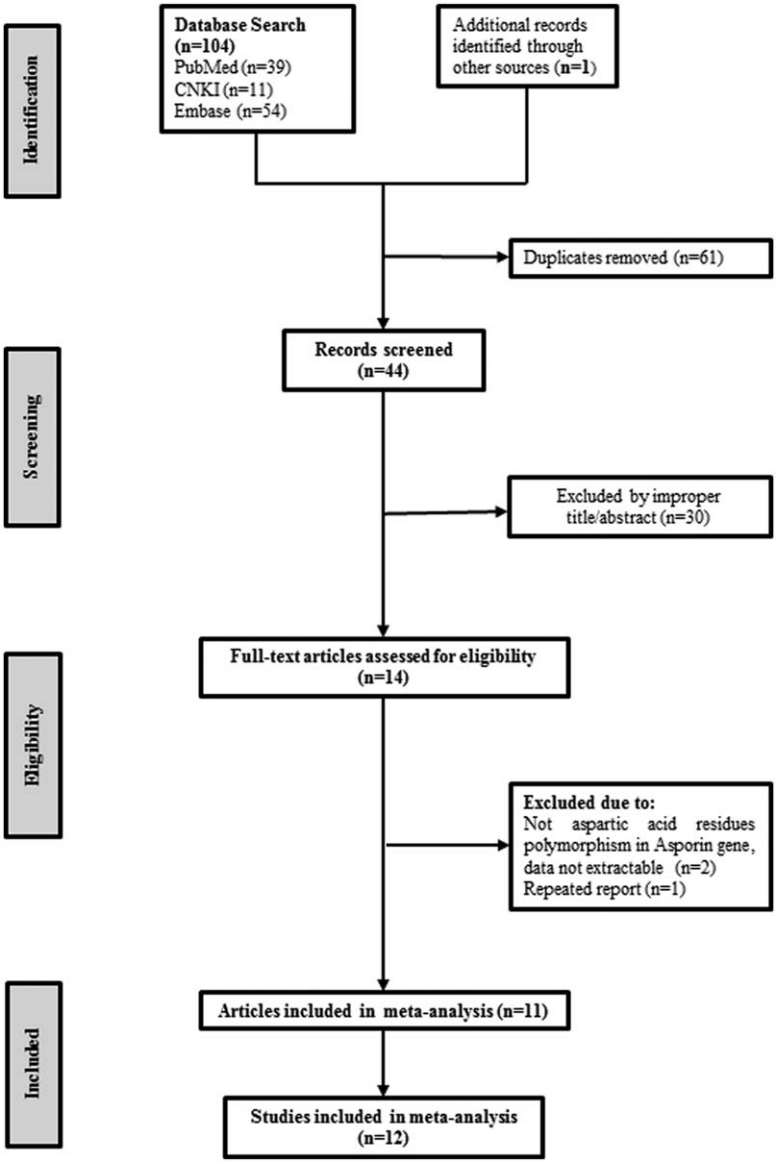

Figure 1. The summary of study search and selection.

OA.[14–24] 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.[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-controled 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

Table 1

Characteristics of the included studies.

First author	Year	Country	Ethnicity	Study design	Eligible subjects (n)		Age (*y*)		Joint affected
					OA	Control	OA	Control	
Kizawa 1[14]	2005	Japan	Asian	Cohort	137	234	NA	NA	Knee
Kizawa 2[14]	2005	Japan	Asian	Case-control	986	374	NA	NA	Knee, hip
Mustafa[15]	2005	UK	Caucasian	Case-control	1247	748	NA	NA	Knee, hip
Kaliakatsos[16]	2006	Greece	Caucasian	Case-control	158	193	68.60	68.60	Knee
Rodriguez-Lopez[17]	2006	Spain	Caucasian	Case-control	723	294	>55	>55	Knee, hip, hand
Jiang[18]	2006	China	Asian	Case-control	218	454	58.10	56.30	Knee
Atif[19]	2008	USA	Caucasian	Case-control	775	511	68.20	70.80	Knee/Hand
Song[20]	2008	Korea	Asian	Case-control	190	376	60.00	47.70	Knee
Arellano[21]	2013	Mexico	Latin American	Case-control	218	222	57.99	52.67	Knee
Jazayeri[22]	2013	Iran	Asian	Case-control	100	100	63.00	63.00	Knee
Arellano[23]	2014	Mexico	Latin American	Case-control	130	130	59.05	53.83	Knee
Gonzalez-Huerta[24]	2015	Mexico	Latin American	Case-control	93	118	56.40	51.80	Knee

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

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 D-repeat polymorphism and susceptibility to knee OA and hip OA in the Asians, Caucasian, 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 I^2 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 2

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

Group	Author	Case					Control				
		Count			Frequency		Count			Frequency	
		D13	D14	Others	D13	D14	D13	D14	Others	D13	D14
Asian	Kizawa Cohort[14]	163	30	81	0.59	0.11	314	22	81	0.67	0.05
	Kizawa Case-control[14]	1190	155	627	0.60	0.08	479	36	627	0.64	0.05
	Jiang[18]	300	41	95	0.69	0.09	604	44	95	0.67	0.05
	Song[20]	265	22	93	0.70	0.06	483	65	93	0.64	0.09
	Jazayeri[22]	82	32	86	0.41	0.16	91	40	86	0.46	0.20
Total		2000	280	982	0.61	0.09	1971	207	982	0.62	0.07
Caucasian	Mustafa[15]	1183	352	959	0.47	0.14	752	190	959	0.50	0.13
	Kaliakatsos[16]	118	47	145	0.38	0.15	189	53	145	0.50	0.14
	Rodriguez-Lopez[17]	627	172	649	0.43	0.12	248	74	649	0.42	0.13
	Atif[19]	749	206	595	0.48	0.13	496	142	595	0.49	0.14
Total		2677	777	2348	0.46	0.13	1685	459	2348	0.38	0.10
Latin American	Arellano[21]	205	91	140	0.47	0.21	204	107	140	0.46	0.24
	Gonzalez-Huerta [24]	7	123	56	0.04	0.66	6	134	56	0.03	0.57
	Arellano-Perez-Vertti[23]	85	49	78	0.40	0.23	85	51	78	0.41	0.24
Total		297	263	274	0.36	0.32	295	292	274	0.34	0.34
χ^2					337.02					485.38	
P					<.001					<.001	

ASPN = asporin.

Table 3

Summary OR and 95% CI of the D-repeat polymorphism and OA susceptibility.

			Test of association			Test of heterogeneity		
Polymorphism	Population	No. of studies	OR	95% CI	*P* value	Model	I^2	*P* value
D13 VS others combined	Overall	12	0.94	(0.89, 0.99)	0.027	Fixed	39.90%	.046
	Asian	5	0.93	(0.78, 1.10)	0.130	Random	62.10%	.022
	Caucasian	4	0.93	(0.87, 1.00)	0.064	Fixed	41.70%	.072
	Latin American	3	1.04	(0.84, 1.29)	0.740	Fixed	0.00%	.771
Knee OA	Overall	12	0.92	(0.82, 1.03)	0.159	Random	51.70%	.019
	Asian	5	0.93	(0.75, 1.16)	0.530	Random	69.50%	.011
	Caucasian	4	0.87	(0.73, 1.04)	0.118	Random	61.10%	.053
	Latin American	3	1.04	(0.84, 1.29)	0.740	Fixed	0.00%	.771
Hip OA	Overall	3	0.92	(0.84, 1.02)	0.116	Fixed	0.00%	.501
	Caucasian	2	0.93	(0.83, 1.05)	0.233	Fixed	23.40%	.253
D14 VS others combined	Overall	12	1.13	(0.98, 1.31)	0.102	Random	62.30%	.000
	Asian	5	1.39	(0.93, 2.09)	0.111	Random	78.00%	.000
	Caucasian	4	1.04	(0.93, 1.16)	0.494	Fixed	0.00%	.583
	Latin American	3	1.04	(0.73, 1.49)	0.838	Random	61.50%	.074
Knee OA	Overall	12	1.15	(0.95, 1.40)	0.151	Random	66.50%	.001
	Asian	5	1.33	(0.80, 2.21)	0.267	Random	81.60%	.000
	Caucasian	4	1.05	(0.90, 1.22)	0.558	Fixed	0.00%	.699
	Latin American	3	1.04	(0.73, 1.49)	0.838	Random	61.50%	.074
Hip OA	Overall	3	1.13	(0.77, 1.66)	0.543	Random	78.00%	.011
	Caucasian	2	0.95	(0.63, 1.44)	0.815	Random	75.00%	.045
D14 VS D13	Overall	12	1.14	(0.98, 1.33)	0.097	Random	59.60%	.001
	Asian	5	1.43	(0.96, 2.12)	0.081	Random	75.90%	.001
	Caucasian	4	1.07	(0.96, 1.20)	0.271	Fixed	8.70%	.363
	Latin American	3	0.88	(0.67, 1.15)	0.338	Fixed	0.00%	.901
Knee OA	Overall	12	1.17	(0.95, 1.43)	0.140	Random	63.10%	.002
	Asian	5	1.37	(0.83. 2.25)	0.217	Random	80.00%	.001
	Caucasian	4	1.10	(0.94, 1.29)	0.232	Fixed	0.00%	.432
	Latin American	3	0.88	(0.67, 1.15)	0.338	Fixed	0.00%	.901
Hip OA	Overall	3	1.15	(0.78, 1.70)	0.474	Random	76.40%	.014
	Caucasian	2	0.98	(0.63, 1.52)	0.914	Random	75.90%	.042

CI = confidence interval, OA = osteoarthritis; OR = odds ratios.

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 others 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: 0.88–1.01, $P = .100$). 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.[1,31–33] 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 studies 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 biomineralization 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.[28] For the D13 allele, OR, and 95% CI in combined population indicated a boderline association (OR = 0.94, 95% CI: 0.89–0.99, $P = .027$), which was inconsistent with other meta-analyses.[26,28] 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.

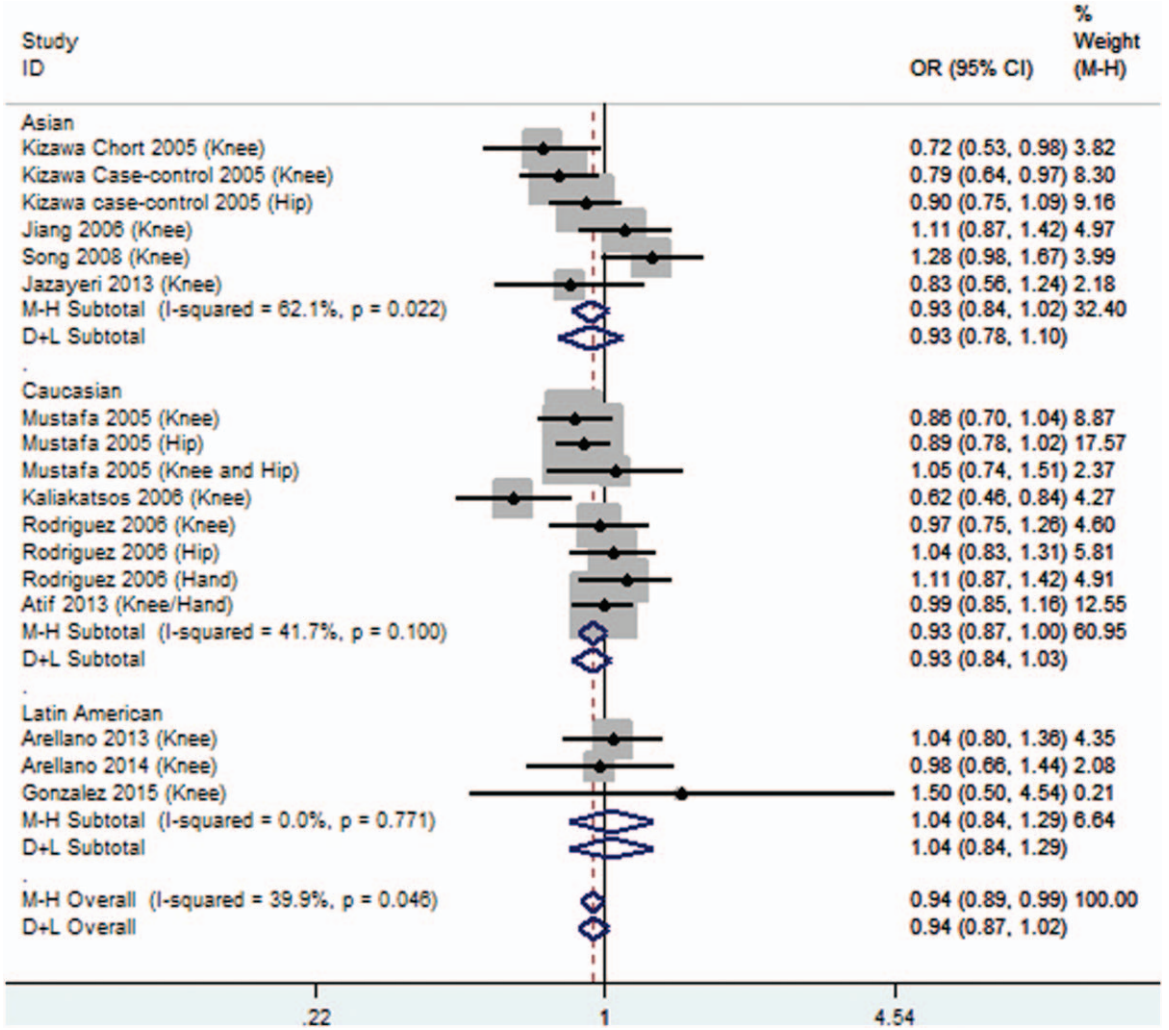

Figure 2. Forest plot of ASPN D-repeat polymorphism and OA for the comparison of D13 allele versus other alleles combined. ASPN = asporin, OA = osteoarthritis.

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

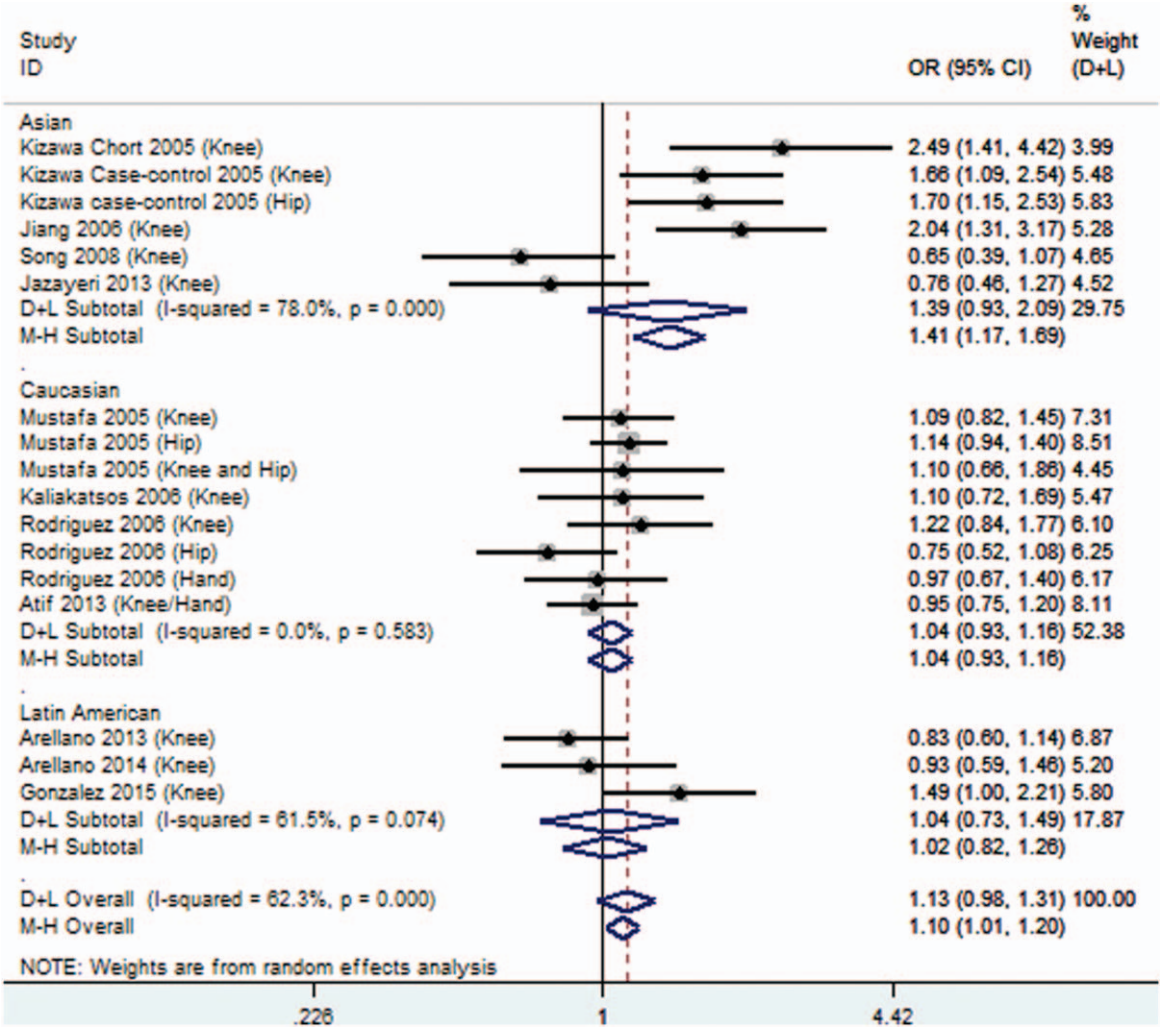

Figure 3. Forest plot of ASPN D-repeat polymorphism and OA for the comparison of D14 allele versus other alleles combined. ASPN = asporin, OA = osteoarthritis.

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.

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