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Association between aspartic acid repeat polymorphism of the asporin gene and risk of knee osteoarthritis: A systematic review and meta-analysis

Mohammad Reza Sobhan [a], Masoud Mehdinejad [b, *], Mohammad Hossein Jamaladini [a], Mahta Mazaheri [c], Masoud Zare-Shehneh [c], Hossein Neamatzadeh [c, d]

[a] Department of Orthopedics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[b] Department of Orthopedics, Afshar Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[c] Department of Medical Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[d] Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

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ABSTRACT

Objective: Studies have assessed the association between aspartic acid (D)-repeat polymorphism in the gene encoding Asporin (ASPN) and knee osteoarthritis (KOA) risk, but the results were inconclusive and contradictory. Therefore, we performed a meta-analysis to investigate the association between ASPN gene D-repeat polymorphism and KOA risk.

Methods: Eligible studies were identified by searching several electronic databases for relevant reports published before September 2016. The pooled odds ratios (ORs) for the association between ASPN polymorphism and KOA and their corresponding 95% confidence intervals (CIs) were estimated using the random- or fixed-effect model.

Results: A total of eleven case-control studies in ten publications with 4610 KOA cases and 3621 controls were included for the ASPN D-repeat polymorphism. Overall, no significant association was detected for D14 allele carrier (D14 vs. D13: OR = 1.10, 95% CI = 0.90–1.36, p = 0.32). Meta-analysis of D14 vs. other alleles and D13 vs. other alleles showed the same pattern of KOA association as the D14 vs. D13 (OR = 1.30, 95% CI = 1.00–1.70, p = 0.06; OR = 0.93, 95% CI = 0.82–1.06, p = 0.33, respectively). Also, in the stratified analysis by ethnicity, no significant association of this polymorphism with risk of KOA was found in the European and Asians populations (OR = 1.05, 95% CI = 0.91–1.21, p = 0.49; OR = 0.98, 95% CI = 0.78–1.23, p = 0.88, respectively).

Conclusions: The present meta-analysis suggests that the ASPN D-repeat polymorphism is not associated with an increased KOA risk. However, future large studies with gene–gene and gene–environment interactions are needed to validate these findings.

Level of evidence: Level III diagnostic study.

Introduction

Osteoarthritis (OA) is a widespread and degenerative, chronic disease that affects up to 80% of the older adults.[1] According to the World Health Organization, more than 150 million people suffer from OA worldwide.[2] Knee OA (KOA) is a common form of arthritis usually occurs in one or both knee joints. According to the studies, KOA is likely to become the fourth most common cause of disability in women and the eighth most common cause in men.[3] KOA is more important not only for its high prevalence rate compared with other types of OA but also for its presentation at earlier age groups particularly in younger age groups of obese women.[4] The KOA-related symptoms have a major impact on subject social and physical wellbeing, and KOA is expected to be the fourth leading cause of disability in 2020.[5]

* Corresponding author.
E-mail address: hn_1364@yahoo.com (M. Mehdinejad).
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The strongest most prevalent risk factors for the incidence of KOA are overweight or obesity, a higher age, and female sex.[5,6] However, in the recent years the model of KOA has changed dramatically and presently considered as a condition influenced by genetics and environmental factors.[7] The heritability estimates showing that genetic components account for 39–65% of the risk for the development of KOA.[8,9] However, it shown that the genetic contribution to KOA in sibling pairs may be much less than at other sites, such as the hips, hands and spine.[10] Specific locus such as *GDF-5*, *7q22* locus, *MCF2L*, *DOT1L*, *NCOA3* has been reported to increase the incidence of KOA, and in recent studies the importance of few specific alleles was confirmed.[8,10,11] However, identification of genetic variants robustly associated with KOA at a genome-wide significant level has been more difficult than for other diseases.[12]

A number of studies have investigated the association between aspartic acid (D) repeat polymorphism of Asporin (ASPN) gene and the risk of KOA in different populations,[13–21] but the results are inconsistent. For instance, four studies from in Mexican, Iranian, Japanese, and Han Chinese Asian populations detect an association with KOA.[13,16,19,20] An earlier meta-analyses failed to detect any association between ASPN D-repeat polymorphism and the risk of KOA in Asians and Caucasians.[22] Since then, multiple studies on the relationship of KOA with ASPN D-repeat have been published. Therefore, the aim of this study was to determine the overall association between ASPN D-repeat polymorphism and KOA risk and whether the association varies by ethnicity.

Materials and methods

Study identification and selection

Eligible studies were identified by searching the relevant literature published before 20 September 2016 by searching databases of PubMed, EMBASE, Web of Science and Google Scholar. The main search terms were “Osteoarthritis”, “Knee osteoarthritis” or “KOA”, “Asporin gene”, “ASPN”, “D-repeat”, “genetic polymorphism”, and “variation”. The extracted publications were limited to English language and conducted on human subjects. We also have read completely all extracted articles and used a hand search of references of original studies or reviewed articles on this topic to identify additional studies.

Inclusion and exclusion criteria

Studies included to the meta-analysis had to be consistent with the following criteria: the study (1) evaluated the association between ASPN and the risk of KOA; (2) used a case-control and cohort design; (3) included a full-text article and; (4) offered the size of the sample and sufficient data (genotypes and allele distributions of both cases and controls) for estimating an odds ratio (OR) with a 95% confidence interval (CI); and (5) used the English language. Exclusion criteria were as follows: the study (1) used only case group data, (2) without definite information of genotypes and alleles (3) reviews, letters or case reports; (4) duplicate publications of data from the same study.

Data extraction

Based on the inclusion and exclusion criteria, the following data were extracted by two investigators independently from each study: the first author, year of publication, genotyping methods, number of KOA patients and controls, genotype and allele frequency. For conflicting evaluation, these two authors carried out discussions until a consensus was reached. If they could not reach a consensus, disagreements were resolved by discussion.

Statistical methods

The crude ORs and their 95% CIs were calculated to assess the strength of the association between ASPN and KOA risk. The pooled ORs were performed for D14 allele vs. D13 allele, D14 allele vs. other alleles combined and D13 allele vs. other alleles combined comparisons. Heterogeneity was assessed for each study using Cochrane's Q test and I^2 measurement. The heterogeneity was considered significant if either the Q statistic had $p < 0.1$ or $I^2 > 50\%$. An I^2 value of 0% represents no heterogeneity, with values of 25%, 50%, 75%, or more represent low, moderate, high, and extreme heterogeneity, respectively.[23] A p value greater than 0.10 indicated a lack of heterogeneity among studies, so the fixed effect model (Mantel–Haenszel method) was used to calculate pooled OR. Otherwise, the fixed-effects model (Mantel–Haenszel approach) was used.[24] One-way sensitivity analyses were carried out by consecutively omitting one study at a time to assess the power of the meta-analysis findings.[25] Visual inspection of the asymmetry of funnel plots was carried out to assess potential publication bias. Begg's funnel plot, a scatter plot of effect against a measure of study size, was generated as a visual aid to detect bias or systematic heterogeneity.[26] The Egger's linear regression test was used to evaluate possible publication bias of studies, and it was regarded as statistically significant when $p < 0.05$.[27] All the statistical analyses were performed by comprehensive meta-analysis (CMA) 2.0 Software (Biostat, USA). Two-sided p values <0.05 were considered statistically significant.

Results

Study selection and characteristics

A total of 15 results were returned through PubMed and Google Scholar. Three articles were excluded after reviewing the titles and abstracts, one study excluded due to the in Chinese language[28]; another 1 study was removed owing to insufficient data after reviewing the full text[29] (Fig. 1). Finally, a total of ten publications[13–21,30] (ten case-control studies and one cohort) examined the associations between ASPN gene D14 and D13 allele polymorphism with KOA risk, including 4610 cases and 3621 controls were selected for the meta-analysis. These studies were published from 2005 to 2015. Two out of 10 publications were conducted in the Mexico, 1 in Japan (included one case control and one cohort study), 1 in USA, 1 in UK, 1 in Spain, 1 in Greece, 1 in China, 1 in Korea and 1 in Iran. All of the articles were written in English. The study characteristics were presented in Table 1.

ASPN D13 and D14 allele polymorphism

The distributions of allele frequencies in each case-control study are shown in Table 1. Meta-analysis showed no association between KOA and the ASPN D14 allele in the overall population (OR 1.10, 95% CI 0.90–1.36, $p = 0.32$). Furthermore, stratification by ethnicity failed to identify any association between this polymorphism and KOA in the European and Asians populations (OR 1.05, 95% CI 0.91–1.21, $p = 0.49$; OR 0.98, 95% CI 0.78–1.23, $p = 0.88$, respectively) (Fig. 2). However, high heterogeneity was found in Asians than European ($I^2 = 81.2$, $P_H = 0.01$; $I^2 = 8\%$, $P_H = 0.36$, respectively). Meta-analysis of D14 vs. other alleles showed the same pattern of KOA association as the D14 vs. D13 (OR 1.30, 95% CI 1.00–1.70 $p = 0.06$). No association was found between the ASPN D13 vs. other alleles and risk of developing KOA by meta-analysis (OR 0.93, 95% CI 0.82–1.06, $p = 0.33$) (Table 2, Fig. 2).

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