Int J Clin Exp Med 2015;8(6):9430-9437
www.ijcem.com /ISSN:1940-5901/IJCEM0009053

Original Article

Association between genetic variants of *DVWA* and osteoarthritis of the knee and hip: a comprehensive meta-analysis

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Received April 13, 2015; Accepted June 10, 2015; Epub June 15, 2015; Published June 30, 2015

Abstract: Recently, double von Willebrand factor domain A (DVWA) gene, a previously unknown gene, was revealed to contain several single nucleotide polymorphisms (SNPs) that showed consistent association with knee osteoarthritis (OA) in Japanese and Chinese cohorts. However, subsequent studies failed to confirm this result in several different populations. To deal with the issues raised by inconsistent results among those studies, we investigated the association between *DVWA* and OA using meta-analytic techniques, combining all published data up to December 2014. 10 independent samples from 4 teams contributed data for a possible association between SNP rs7639618 and knee or hip OA. The total number of cases and controls of this SNP was respectively 4,142 versus 6,575 for knee OA, and 2,325 versus 2,914 for hip OA. A trend of significant association was observed in the combined population with knee OA (P=0.06), and a significant difference was identified between patients with knee OA and controls for the G-allele of rs7639618 (P=0.02). Together with the reported functional studies, our results indicate that *DVWA* may have a small but strong effect on the susceptibility to knee OA, at least in Asian population. Further functional studies are needed to determine the underlying variation of *DVWA* and to relate this to the pathophysiology of OA.

Keywords: Osteoarthritis, DVWA, SNP, association, meta-analysis

Introduction

Osteoarthritis (OA, MIM 165720), the most common age-related degenerative disease of the synovial joint, is characterized by cartilage degradation, formation of osteophytes, and subchondral sclerosis [1]. Heritability studies of twins, sibling pairs, and families have highlighted the possibility that OA is a complex disease of the musculoskeletal system with both genetic and environment risk factors. Based on previous studies, genetic factors are estimated to account for about 50% of the risk of developing OA in the knee, hip, or hand, although precise estimates vary according to affected site, severity of disease, etc [2-4]. Therefore, a substantial proportion of variation in risk of OA can be attributed to genetic variation, i.e., polymorphisms in genes involved in the etiology of OA. Identifying these susceptibility genes could provide new clues to the pathophysiology of OA and might lead to new therapeutic targets [1, 5].

Recently, thanks to a genome wide association (GWA) study, a previously unknown gene coding for double von Willebrand factor domain A (DVWA), was revealed to contain several single nucleotide polymorphisms (SNPs) that showed consistent association with knee OA in Japanese and Chinese case-control cohorts. The highest association was found for *DVWA* SNP rs7639618 [6, 7]. This particular SNP has been shown by Miyamoto *et al*. to be one of the two non-synonymous *DVWA* SNPs that influence DVWA binding to β-tubulin, the other one being rs11718863 [6]. This association was supported by results on a UK sample [7], but other studies failed to confirm this result in Dutch, Spainish, Greek, British and Korean pop-

Table 1. Characteristics of the included studies for SNP rs7639618 and knee OA

Study	Country	Sample	Genotypes			X^2	*P*-value[a]	HWE	Alleles		X^2	*P*-value[a]
			GG	GA	AA			*P*-value[a]	G	A		
Miyamoto *et al*., 2008	Japan 1	Cases	253	293	95	30.33	**0.00000026**		799	483	28.98	**0.0000001**
		Controls	162	327	140			>0.05	651	607		
	Japan 2	Cases	99	107	36	4.04	0.132		305	179	4.29	**0.038**
		Controls	166	222	95			>0.05	554	412		
	China	Cases	145	187	85	10.61	**0.005**		477	357	11.43	**0.0007**
		Controls	106	192	115			>0.05	404	422		
Meulenbelt *et al*., 2009	UK	Cases	275	85	6	5.71	0.057		635	97	5.55	0.019
		Controls	504	215	19			>0.05	1223	253		
	Netherlands	Cases	98	36	3	0.17	0.916		232	42	0.13	0.715
		Controls	538	188	13			>0.05	1264	214		
	Spain	Cases	171	72	6	2.0	0.368		414	84	0.04	0.839
		Controls	189	70	12			>0.05	448	94		
	Greece	Cases	280	80	8	1.07	0.586		640	96	1.11	0.292
		Controls	291	97	11			>0.05	679	119		
Valds *et al*., 2009	UK1	Cases	188	68	8	0.68	0.713		444	85	0.01	0.903
		Controls	357	143	12			>0.05	857	167		
	UK2	Cases	505	201	27	6.01	**0.0496**		1211	255	3.99	**0.046**
		Controls	474	169	11			>0.05	1117	191		
Lee *et al*., 2013	Korea	Cases	212	374	139	1.24	0.538		798	652	0.10	0.755
		Controls	519	857	361			>0.05	1895	1579		

[a]Significant *P* values (<0.05) are in boldface.

ulations [7-9]. There are some explanations for this heterogeneity of results. First in the research of susceptibility loci for OA, it has become apparent that some of them are particularly associated with one specific skeletal site. Second, OA genetic component is known to be partly driven by ethnicity. For this reason, polymorphisms that are shown to be significant in Asian populations may not be significant in European populations, and vice versa [7, 10-14]. To deal with the ambiguities raised by inconsistent results among molecular genetic studies, the statistical method of meta-analysis, which could provide an effective way to assess size effects in different independent studies while addressing the heterogeneity between them, was suggested to be used [15].

In the current study, a comprehensive meta-analysis using all published association studies was performed to assess the global effect of *DVWA* susceptibility on common phenotype of OA across different ethnic groups.

Materials and methods

Data source

To identify studies eligible for meta-analysis, PUBMED (http://www.ncbi.nlm.nih.gov), SCOPUS (http://www.scopus.com), and EMBASE (http://www.elsevier.com/online-tools/embase) (up to Dec 2014) were surveyed with "Osteoarthritis", "Double von Willebrand factor domain A", "OA" and "DVWA" as keywords. The abstracts retrieved were read to identify studies that examined an association between a polymorphism within the *DVWA* locus and OA. Those articles were then read in their entirety to assess their appropriateness for inclusion in the meta-analysis. All references cited in these studies were also reviewed to identify additional studies not indexed by PUBMED, SCOPUS and EMBASE.

Inclusion criteria and exclusion criteria

All the included studies had to meet all of the following criteria: (1) to be published in a peer-reviewed journal; (2) to test at least one polymorphism within the *DVWA* gene locus; (3) to present original data on genotype and allele distribution, mentioning genotype frequencies to test for Hardy-Weinberg equilibrium among controls; (4) to be independent one from the other (no overlaps between subject groups of the different studies); and (5) to contain sufficient data to calculate an effect size [16, 17]. Moreover, only studies published in English were included.

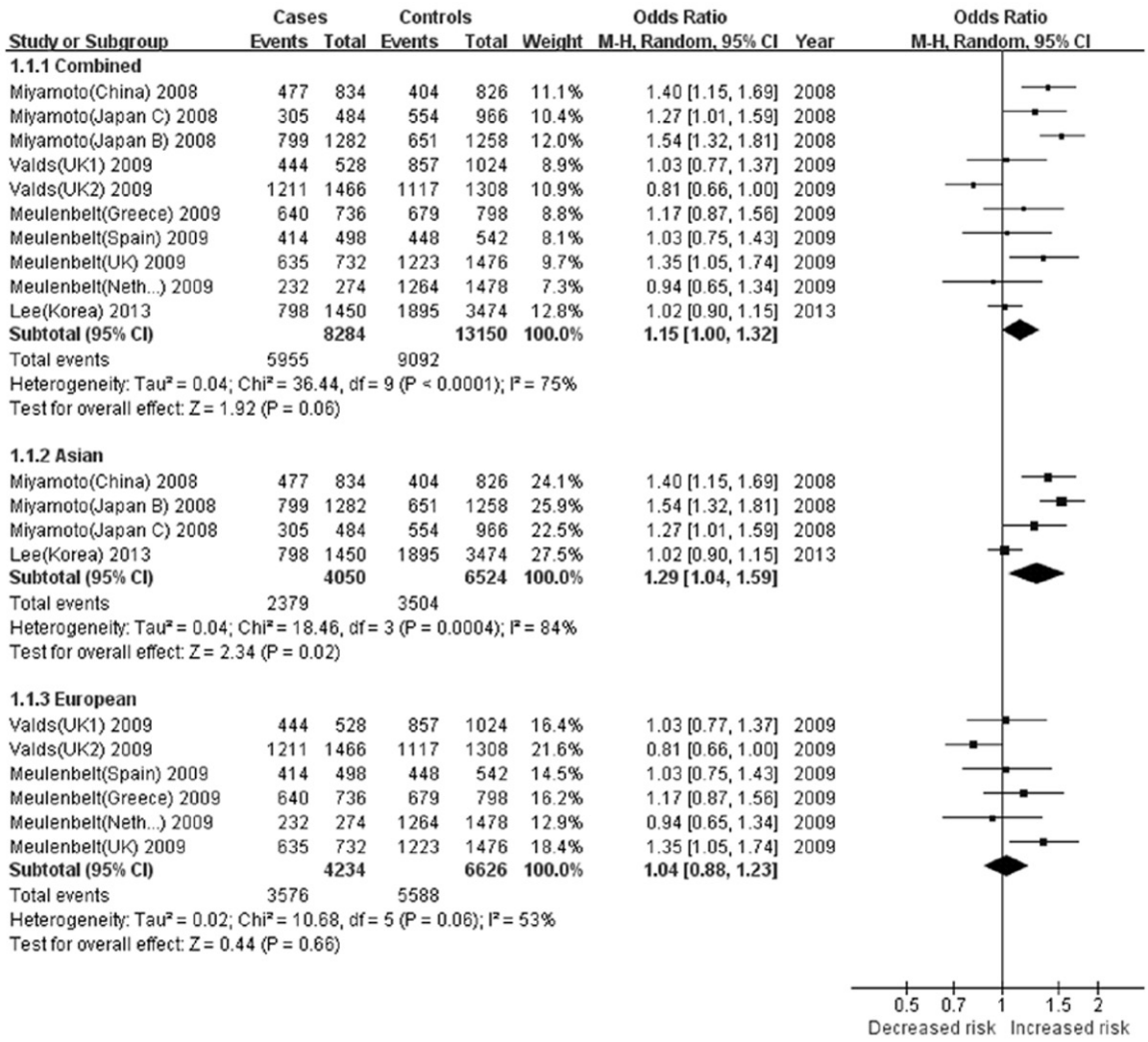

Figure 1. Meta-analysis of the association of rs7639618 and knee OA.

Phenotype definitions based on clinical criteria and radiographic criteria were accepted. The American Rheumatism Association criteria were chosen as clinical criteria. The Kellgren/Lawrence (K/L) classification system was chosen as radiographic criteria. This system is the most widely used scale for identifying and grading OA (scores 0-4, with 0 representing normal findings and 4 representing severe OA). A K/L score ≥2 was used to define OA, unless the data had been generated with another cutoff and the definition could not be revisited [18].

Studies presenting non-original data were excluded, such as reviews, opinion papers or editorials. Studies in which rheumatoid, inflammatory, or other forms of arthritis were incorporated in the OA datasets were excluded. Studies with no extractable, numerical data were excluded. Studies using non-human subjects or specimens were excluded. Any duplicates which came up in the preliminary search were excluded [17].

Data extraction

The following information was extracted by two independent investigators from the eligible studies: (1) first author; (2) journal; (3) year of publication; (4) study design; (5) ethnicity of the subjects; (6) sample size; (7) phenotype information; (8) genotype and allele distribution of subjects with and without OA. For genetic association studies with conflicting results on the same genetic variants, the quality of study design should be controlled by appropriate cri-

Table 2. Characteristics of the included studies for SNP rs7639618 and hip OA

			Genotypes					HWE	Alleles			
Study	Country	Sample	GG	GA	AA	X^2	*P*-value[a]	*P*-value[a]	G	A	X^2	*P*-value[a]
Meulenbelt *et al*., 2009	UK	Cases	808	288	20	4.16	0.125		1904	328	4.02	**0.045**
		Controls	504	215	19			>0.05	1223	253		
	Netherlands	Cases	67	31	1	1.76	0.414		165	33	0.66	0.415
		Controls	538	188	13			>0.05	1264	214		
	Spain	Cases	175	84	8	2.58	0.275		434	100	0.35	0.555
		Controls	189	70	12			>0.05	448	94		
Valds *et al*., 2009	UK1	Cases	34	15	1	0.11	0.945		83	17	0.03	0.859
		Controls	357	143	12			>0.05	857	167		
	UK2	Cases	544	234	15	2.58	0.275		1322	264	2.26	0.133
		Controls	474	169	11			>0.05	1117	191		

[a]Significant *P* values (<0.05) are in boldface.

teria to limit the risk of introducing bias into meta-analyses. Therefore, the phenotypes of OA, i.e., knee, hip and hand OA, were addressed separately.

Statistical analysis

Association studies were collected and subdivided into Asian and European ethnic populations. Data on genotype and allele distribution were summarized in tables. HWE was assessed separately in the control group of each studies. *P*-value significance threshold for deviation from HWE was set to $P<0.05$. Allele frequencies were analyzed by Chi-square test using the Epi_Info program (http://www.cdc.gov/epiinfo), and classical threshold of $P<0.05$ was chosen to define statistically significance.

Prior to the pooling procedure, Cochran's Q statistic (Chi-square test), which is considered significant at $P<0.10$, was performed in order to assess heterogeneity within the group of odds ratios (OR). The natural logarithms of the OR estimates were synthesized using random-effects models and fixed-effects models. In random-effects models, the risk allele effects of each study are assumed to vary around some overall average effect, and the heterogeneity among studies is taken into account. Fixed-effects models assume that the true genetic effect of the risk allele is constant among groups and that the observed differences are due to chance [18]. The two models coincide except when heterogeneity between studies exists: in this case, the random-effects models yields wider confidence intervals (CIs). The significance of the pooled OR was determined by the Z-test. Sensitivity analysis, which determines the influence of individual studies on the pooled OR, was determined by sequentially removing each study and recalculating the pooled OR and 95% CI by Z-test [16]. All statistical analyses were performed using the software program RevMan version 5.2 (http://www.cochrane.org/revman) [19].

Results

Available studies

At least 17 references were identified by the combined search. After discarding reviews and studies that did not meet the criteria, 10 references were left. Moreover, 5 references were excluded as they were not genetic association studies of SNPs. Since only one association study yielded a negative association between rs7639618 and hand OA, we didn't perform a meta-analysis for hand OA [20]. A family-based meta-analysis could not be performed as no family-based association study was reported. Finally, 4 independent case-control studies that were combined to perform a meta-analysis on association between SNP rs7639618 and knee or hip OA [6-9]. Three of these four studies provided data from more than two different samples [6-8]. In the end, the total number of cases and controls for SNP rs7639618 was respectively 4,142 versus 6,575 for knee OA, and 2,325 versus 2,914 for hip OA.

Knee OA

4 previous association studies of SNP rs7639618 with knee OA are summarized in **Table 1**. The controls of every independent sample fulfilled HWE criteria ($P>0.05$). Overall

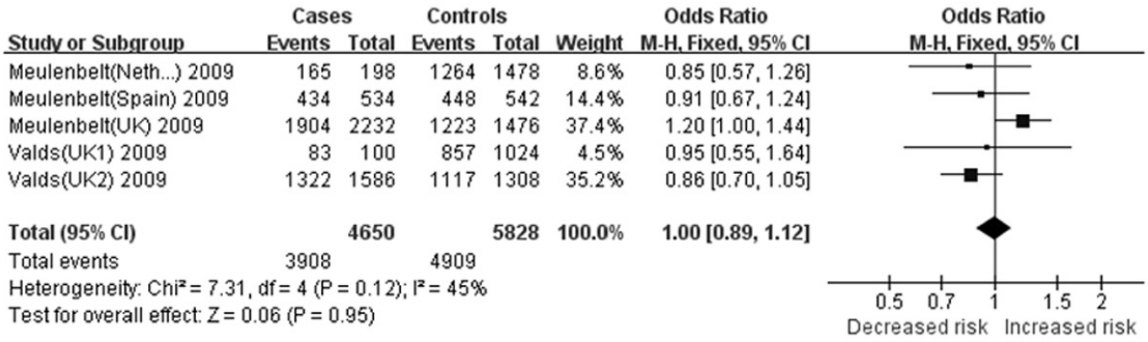

Figure 2. Meta-analysis of the association of rs7639618 and hip OA.

4,142 cases and 6,575 controls were analyzed. Concerning allele-wise analysis significant evidence of between-study heterogeneity was found (X^2=36.44, *df*=9, *P*<0.0001). Using a random-effect model, a trend toward significance was identified between patients and controls for the G-allele of rs7639618 (subtotal OR=1.15, 95% CI=1.00-1.32, Z=1.92, *P*=0.06) (**Figure 1**). We further separately analyzed studies by ethnicity (i.e., Asian and European), in order to limit ethnic heterogeneity.

In the Asian samples, the random-effect meta-analysis was used because of the heterogeneity (X^2=18.46, *df*=3, *P*=0.0004). A significant difference was found between cases and controls (Subtotal OR=1.29, 95% CI=1.04-1.59, Z=2.34, *P*=0.02). In the European samples, the homogeneity test of the meta-analysis showed significant heterogeneity (X^2=10.68, *df*=4, *P*=0.06). No significant difference was found between patients and controls under the random-effects method (subtotal OR=1.04, 95% CI=0.88-1.23, Z=0.44, *P*=0.66) (**Figure 1**). It is interesting to note that we observed an important difference of allele frequency between Asians and Europeans for SNP rs7639618. Frequency of the G-allele of this marker was ~55% in Asians (58.7% in cases and 53.7% in controls) versus ~84% in Europeans (84.5% in cases and 84.3% in controls) (data not shown).

Sensitivity analysis showed that removal of any of the studies did not deeply change the heterogeneity of the population either in combined sample or in European samples. However, when we removed the study by Lee *et al.* from Asian samples, the estimates of the *P* value for the homogeneity test increased from 0.0004 to 0.36, suggesting that the genetic heterogeneity was mainly caused by the data from this study. Meanwhile, the *P* value of Z-test was also increased sharply (0.02 to <0.00001) (data not shown).

Hip OA

Table 2 shows the detailed data of association studies between rs7639618 and hip OA. Two teams, including five European samples, contributed 2,325 cases and 2,914 controls. The fixed-effects model were performed in meta-analysis, as no heterogeneity was observed in combined studies (X^2=7.31, *df*=4, *P*=0.12). Non-statistically significant summary OR was found in European studies (subtotal OR=1.00, 95% CI=0.89-1.12, Z=0.06, *P*=0.95) (**Figure 2**). In addition, when we performed sensitivity analysis, between-study heterogeneity was not changed deeply.

Discussion

DVWA, a previously unknown gene, was identified to be associated with knee OA in Japanese and Chinese subjects. At least two SNPs, rs7639618 (encoding C260V) and rs11718863 (encoding Y169N) showed strongly significant association with this disease [6]. In the current meta-analysis, we investigated the rs7639618 polymorphism on *DVWA* locus with OA to assess the global effect by using 10 independent samples from 4 published references.

A trend toward significance was observed in the combined population (*P*=0.06), suggesting a potential association of rs7639618 with knee OA. After stratification by ethnicity (Asian and European), the results of the association tests for this particular SNP were different for these

groups (P=0.02 and P=0.66, respectively), providing further evidence for association with knee OA in the Asian population, but not in the European population. These results are in line with several previous studies [6-8]. There is a reasonable explanation for above findings: OA is heterogeneous, with the markers in different ethnic groups having different informational content [21]. Allelic distribution of rs7639618 was significantly different in the Asian controls (53.7% of G-allele) compared to European controls (84.3% of G-allele).

In addition, no significant difference between rs7639618 and hip OA was revealed in the combined European samples (P=0.95). This result is consistent with the studies of Valdes *et al*. and Meulenbelt *et al*. [7, 8]. Unfortunately, no further comparison could be performed between Asians and Europeans for rs7639618 with hip OA, since no relevant association study was reported in Asians.

As mentioned earlier, it is a common phenomenon that many susceptibility loci for OA showed particular relevance in different ethnic populations to disease development at particular skeletal sites. For example, the association of the *CALM1* promoter variant with hip OA in Japanese cohort was not replicated in any of the European samples [22, 23]. Similarly, no evidence for association of *EDG2* promoter variant with OA in European subjects was found, although the SNP had been reported to be strongly associated with knee OA in Japanese samples [8, 24, 25]. Such lack of repeatability of Asian associations in European subjects may have several explanations, including genetic heterogeneity or even environmental differences between two groups in the risk of OA [8].

In the previous studies, DVWA protein is predicted to have two domains homologous to the VWA domain, and mutations in the VWA domains of *MATN3* could cause OA [6, 26]. Meanwhile, based on examination of *DVWA* expression in various human tissues, showed that the highest expression was found in cartilage tissues from both OA patients and healthy controls, suggesting that DVWA function is associated with cartilage [6]. A functional study revealed that knockdown of *DVWA* by siRNAs increased expression of chondrocyte matrix genes, indicating the specific role of *DVWA* in human cartilage metabolism [27].

In summary, there is no simple interpretation from our meta-analysis, but a possible conclusion may be that there is a small but strong effect of *DVWA* in susceptibility to knee OA, at least in Asian population. As new studies emerge, the present results can be updated, and more reliable estimates of this association in different ethnic groups may be obtained. Further functional studies are needed to determine the underlying variation of *DVWA* and to relate this to the pathophysiology of OA.

Acknowledgements

We are indebted to all individuals who have participated in, or helped with, our research. This study was supported by the National Natural Science Foundation of China (No. 81272023; No. 81301151; No. 31371298); China Postdoctoral Science Foundation (No. 2013M-542337); Program for New Century Excellent Talents in University (NCET-13-0452); the Key Project of International Scientific Cooperation of Shaanxi Province (No. S2013KW25-02); and the Fundamental Research Funds for the Central Universities (No. 2012JDGZ07; No. XJJ2012124).

Disclosure of conflict of interest

None.

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