Objectives
Degenerative disc disease (DDD) and osteoarthritis (OA) are relatively frequent causes of disability amongst the elderly; they constitute serious socioeconomic costs and significantly impair quality of life. Previous studies to date have found that aggrecan variable number of tandem repeats (VNTR) contributes both to DDD and OA. However, current data are not consistent across studies. The purpose of this study was to evaluate systematically the relationship between aggrecan VNTR, and DDD and/or OA.

Methods
This study used a highly sensitive search strategy to identify all published studies related to the relationship between aggrecan VNTR and both DDD and OA in multiple databases from January 1996 to December 2016. All identified studies were systematically evaluated using specific inclusion and exclusion criteria. Cochrane methodology was also applied to the results of this study.

Results
The final selection of seven studies was comprehensively evaluated and includes results for 2928 alleles. The most frequent allele among all the studies was allele 27. After comparing the distributions of each allele with others, statistically significant differences have been found in the distribution of the alleles by the two groups, with an over-representation of allele (A)21 (disease: 3.22%, control: 0.44%). Thus, carrying A21 increased the risk of DDD. Such an association was not found to be statistically significant when considering the risk of OA.

Conclusions
The findings suggest that VNTR A21 seems to be associated with higher risk to DDD, however, such an association may not be statistically significant regarding the risk of OA.

Cite this article: Bone Joint Res 2018;7:308–317.

Keywords: Degenerative disc disease, Osteoarthritis, Aggrecan variable number of tandem repeats, Meta-analysis

Strengths and limitations
The major strength of this systematic review is that we conducted a comprehensive search of multiple databases, selected and appraised studies by independent pairs of reviewers, and followed an a priori planned protocol that included several hypotheses for the role of aggrecan VNTR in DDD and/or OA.

There are several limitations, namely the quantity of included studies was comparatively small, and thus carrying this allele
may not have a statistically significant effect on the risk of OA.

Introduction

Degenerative disc disease (DDD) and osteoarthritis (OA) are prevalent diseases, which have staggering socioeconomic effects on today’s society and place a heavy burden on global health care. Osteoarthritis is a relatively frequent musculoskeletal problem that causes stiffness and significant pain in the joints. While DDD is considered an inevitable consequence of ageing, and is thought to be one of the most common causes of chronic back pain, together with OA, it results in a significant impairment to quality of life. Despite numerous studies of their aetiology and pathogenesis, it is not clear why the susceptibility to DDD and OA is low in some individuals while high in others.

Intervertebral discs (IVD) and articular cartilage assist load transfer and movement in the spine and joints. In both of these chondroid tissues, an extensive matrix of collagen and aggrecan is maintained by a small population of cells, and although the chondroid tissues are essentially lacking in nerves and blood vessels, both can lead to disability and pain when influenced by degenerative changes. Matrix biology research involving both types of cartilage shows some striking parallels and considerable overlap. The traditional aetiology of DDD and OA and their links with smoking, occupation, age, and obesity, have been well described. Recent literature suggests that the aggrecan content of the IVD and articular cartilage intimately affect their functions. Aggrecan consists of globular domains G1, G2, and G3. There is a long glycosaminoglycan (GAG) attachment region between domains G2 and G3 that consists of adjacent domains of chondroitin sulfate (CS) and keratan sulfate (KS). The glycosaminoglycan chain structures vary throughout life as the CS chains become shorter and KS chains become longer in the adult. This may reflect reduced oxidation of glucose to glucuronic acid, which is needed for CS synthesis, because of the avascular nature of the IVD and articular cartilage. Under normal circumstances, both disc cells and articular chondrocytes maintain a dynamic equilibrium between degradation and synthesis of extracellular matrix components, containing collagen fibrils that form a network surrounding and restraining huge, hydrated aggregates of aggrecan.

The aggrecan gene variable number of tandem repeats (VNTR) polymorphism in a human being has repeats of 57 nucleotides; these encode each 19-amino acid unit. The described alleles of aggrecan VNTR range from 13 to 34 repeats. It has been previously suggested that there is a relationship between aggrecan gene VNTR and DDD and/or OA. Horton et al identified that the allele containing 27 repeats (A27) was statistically associated with bilateral hand OA. Solovieva et al also found that the A26 was statistically associated with lumbar disc degeneration. Other studies reported that A18, A21, and A25 were risk factors for lumbar disc degeneration, whereas A29 was a protective factor for DDD.

Considering these ambiguous results, it is still uncertain which aggrecan VNTR allele is the main risk factor for DDD and/or OA. We have therefore reviewed the literature and performed a meta-analysis to assess systematically the relationship between the aggrecan gene VNTR polymorphism and DDD and/or OA.

Materials and Methods

Search strategy. This study was completed in accord with the guidance outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The databases used for the search were PubMed, Ovid EMBASE, Ovid MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, ACP Journal Club, Scopus and Web of Science, and the Database of Abstracts of Review of Effectiveness. The search covered data from 1996 to December 2016. A combination of text words and controlled vocabulary were used. MEDLINE uses a single term, aggrecan, but EMBASE and others use the terms ACAN or AGC1, but include more specific terms for aggrecan. To be as inclusive as possible, the search also included text words: agcan, cspgcp, and cspg1 (Aggrecan core protein). The same approach was used for osteoarthritis: osteoarthritis is used by MEDLINE, however, EMBASE and others use arthritis with more specific terms including cartilage or chondrocyte. There are similar differences for chondrolysis, remodelling of the subchondral bone versus degeneration of the cartilage. Additionally, the same approach was also used for degenerative disc disease: intervertebral disc is used by MEDLINE, however, EMBASE and others use intervertebral disc, with more specific terms including nucleus pulposus, endplate or annulus fibrosus. It is a similar story for intervertebral disc disease, degeneration, spinal stenosis, and displacement versus herniation. Text words were also used to be inclusive. The results were downloaded into EndNote (EndNote X7, Bld 7072; Thomson ResearchSoft, Stamford, Connecticut), and duplicates removed. The reference lists of all identified studies without language restrictions were reviewed for further identification of potentially relevant articles.

Selection criteria. We systematically identified published articles regarding the relationship between the aggrecan gene VNTR polymorphism and DDD and/or OA according to the following inclusion criteria: Assessing the relationship between aggrecan VNTR polymorphism and
The relationship between the distributions of aggrecan gene VNTR polymorphism and degenerative disc disease/osteoarthritis

DDD and/or OA; cohort design (case-controlled or cross-sectional); full articles only (accordingly, animal studies, case reports, abstracts, conference presentations, reviews, expert opinions, and editorials were excluded); and articles must contain information on allele frequency of the aggrecan VNTR polymorphism or sufficient data for computation of OR (odds ratio) with the corresponding 95% confidence interval (CI). When the relevant information was not available, we contacted the authors to request it.

Data collection. The two investigators (LC and GT) independently extracted data from the text, figures and tables of the included studies using a standardized datasheet. They then selected the eligible cohorts according to the inclusion and exclusion criteria. Disagreements would be dealt with by discussion with the two investigators and, if necessary, by further discussion with another independent co-author. The categories of the extracted data were as follows: author’s name; publication year; participant characteristics (country, source of control subjects, age and ethnicity of the investigated population) and number of participants; study characteristics; numbers of allele frequency in cases and controls; and OR and 95% CI of the comparisons.

Statistical analysis. For each study, we compared every single allele of aggrecan VNTR with other alleles to find the risk allele for DDD and/or OA. This study statistically pooled the data of included studies in order to discover the distribution of aggrecan VNTR. The calculated results were expressed in terms of OR and 95% CI for dichotomous outcomes. Two reviewers checked the collected data, entered them into the computer, and then analyzed the data using Review Manager (RevMan, Version 5.3. Copenhagen, Denmark). The Laird Q test was performed for heterogeneity and the I² statistic was also calculated for each analysis. If a study had a p value \( \leq 0.05 \) and I² \( \geq 50\% \), indicating obvious heterogeneity between studies, the random effects model was performed to evaluate...
the pooled OR.\textsuperscript{16,17} Otherwise, the fixed effects model was used.\textsuperscript{18} We also performed a sensitivity analysis by omitting each study in turn to assess the stability of the results. A p-value \( \leq 0.05 \) was considered statistically significant. All p-values presented are two-tailed. All authors had access to all of the data. We then used the rating system (with levels of evidence 1 through 5) of the Cochrane Back Review Group to assess the level of evidence.\textsuperscript{19,20}

### Results

#### Description of studies

We identified 658 eligible studies by filtering through the inclusion and exclusion criteria (Fig. 1). After initial screening, 460 studies were removed that examined genes, but did not focus on aggrecan. Upon further evaluation of titles and abstracts, 130 additional studies were omitted (Fig. 1). Of the remaining 68 candidate studies, we excluded a further 61 because assessment of the full-text versions revealed that these studies were either reviews,\textsuperscript{5,21-23} or lacked the required allele data\textsuperscript{24} (Fig. 1). The final selection of seven studies was comprehensively evaluated and encompassed results for 2928 alleles, with one set of hand OA and knee OA\textsuperscript{9} discussed in a single multidisciplinary cohort (Tables I and II).\textsuperscript{10-13,25,26}

**Table 1.** Characteristics of included studies when examining the relationship between aggrecan variable number of tandem repeats and degenerative disc disease (DDD) and/or osteoarthritis (OA)

| Author         | Year | Country | Setting | Gender | Age | Disease group | Control group | Risk allele | Protect allele | Size of participants |
|----------------|------|---------|---------|--------|-----|---------------|---------------|-------------|------------------|--------------------|
| Cong\textsuperscript{11} | 2010 | China   | Hospital case-control | Men | 14 to 49 | LDH (n = 70) | Trauma patient (n = 14); Healthy (n = 113) | A21 and A25 | A13 to A27 | 197               |
| Eser\textsuperscript{25} | 2010 | Turkey  | Hospital case-control | Men | 20 to 30 | DDD (n = 150) | None DDD (n = 150) | A29 | None | 300               |
| Horton (hand)\textsuperscript{9} | 1998 | USA     | Hospital case-control | Men | 72.0 (sd 7.1) | Hand OA (43) | None hand OA (n = 50) | A27 | None | 93                |
| Horton (knee)\textsuperscript{9} | 1998 | USA     | Hospital case-control | Men | 72.0 (sd 7.1) | Knee OA (n = 28) | None knee OA (n = 65) | None | None | 93                |
| Kawaguchi\textsuperscript{12} | 1999 | Japan   | Hospital case-control | Men | 20 to 29 | DDD (n = 32) | Normal (n = 32) | A18 and A21 | A26 | 310               |
| Kim\textsuperscript{13} | 2011 | South Korea | Hospital case-control | Women | 13 to 73 | IDD (n = 43) | Normal (n = 12) | A21 | None | 132               |
| Solovieva\textsuperscript{10} | 2007 | Finland | Hospital case-control | Men | 41 to 46 | IDD (n = 116) | None IDD (n = 16) | A27 | None | 530               |
| Kämäräinen\textsuperscript{26} | 2006 | Finland | Hospital case-control | Women | 45 to 63 | Hand OA (n = 281) | Normal (n = 249) | None | None | 530               |

LDH, lumbar disc herniation; IDD, intervertebral disc degeneration.

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The described aggrecan vNTR polymorphism allele frequencies in male and/or female populations. The distribution of each allele, which indicates robustness of this meta-analysis. The number of included studies was less than ten, therefore, we did not assess publication bias. We cannot identify unpublished research with negative results. Publication bias may exist, which could lead to an overestimation of the effectiveness of aggrecan VNTR.

### Discussion

Intervertebral discs (IVD) and articular cartilage assist load transfer and movement in the spine and joints. Aggrecan is the major proteoglycan of IVDs and articular cartilage, and it is present in very high concentrations in the form of aggregates which create osmotic swelling pressure gradients that draw water into the tissue. Recent literature indicates that the aggrecan content of the IVD and articular cartilage intimately affect their functions. The loss of aggrecan has a major effect on both DDD and OA,\textsuperscript{27,28} and there is a relationship between aggrecan gene vNTR and loss of aggrecan. Thus, there could be a common genetic predisposition to both DDD and OA with certain aggrecan
### Table II. Distribution of the aggrecan VNTR alleles among all included studies

| Observed allele repeat, n | Cong | Eser | Horton (hand) | Horton (knee) | Kawaguchi | Kim | Solovieva | Kämäräinen |
|---------------------------|------|------|---------------|---------------|------------|-----|-----------|------------|
|                           | Observed allele repeat, n | Frequency of the disease group, n | Frequency of the control group, n |
| 13                        | 0     | 0    | 0             | 0             | 0          | 0   | 0         | 0          |
| 18                        | 2     | 0    | 0             | 0             | 0          | 0   | 0         | 0          |
| 19                        | 0     | 1    | 2             | 0             | 0          | 0   | 0         | 0          |
| 20                        | 1     | 4    | 0             | 0             | 0          | 0   | 0         | 0          |
| 21                        | 8     | 1    | 13            | 2             | 0          | 0   | 0         | 0          |
| 22                        | 4     | 2    | 13            | 2             | 0          | 0   | 0         | 0          |
| 23                        | 8     | 14   | 25            | 2             | 0          | 0   | 0         | 0          |
| 24                        | 14    | 31   | 25            | 2             | 0          | 0   | 0         | 0          |
| 25                        | 33    | 31   | 28            | 2             | 0          | 0   | 0         | 0          |
| 26                        | 19    | 36   | 43            | 6             | 0          | 0   | 0         | 0          |
| 27                        | 34    | 57   | 90            | 7             | 0          | 0   | 0         | 0          |
| 28                        | 14    | 30   | 63            | 8             | 0          | 0   | 0         | 0          |
| 29                        | 3     | 20   | 33            | 1             | 0          | 0   | 0         | 0          |
| 30                        | 0     | 9    | 0             | 0             | 0          | 0   | 0         | 0          |
| 31                        | 0     | 4    | 0             | 0             | 0          | 0   | 0         | 0          |
| 32                        | 0     | 3    | 1             | 0             | 0          | 0   | 0         | 0          |
| 33                        | 0     | 3    | 0             | 1             | 0          | 0   | 0         | 0          |
| 34                        | 0     | 0    | 0             | 0             | 0          | 0   | 0         | 0          |
| 36                        | 0     | 0    | 0             | 0             | 0          | 0   | 0         | 0          |
| Total                     | 140   | 254  | 300           | 86            | 100        | 56  | 130       | 64         | 24         | 232       | 32       | Total | 448   | 612   |
| Study or Subgroup | Disease Group Events | Control Group Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
|-------------------|----------------------|----------------------|-------|--------|---------------------|---------------------|
| Cong 2010         | 2                    | 140                  | 1     | 254    | 41.7%               | 9.19 [0.44, 192.73] |
| Eser 2010         | 0                    | 300                  | 0     | 300    | Not estimable       | Not estimable       |
| Horton (Hand) 1998| 0                    | 86                   | 0     | 100    | Not estimable       | Not estimable       |
| Horton (Knee) 1998| 0                    | 56                   | 0     | 130    | Not estimable       | Not estimable       |
| Kawaguchi 1999    | 1                    | 64                   | 0     | 64     | 58.3%               | 3.05 [0.15, 6.76]   |
| Kim 2011          | 0                    | 86                   | 0     | 24     | Not estimable       | Not estimable       |
| Solovieva 2007    | 0                    | 232                  | 0     | 32     | Not estimable       | Not estimable       |

Total (95% CI): 964
Total events: 3
Heterogeneity: $\chi^2 = 0.24, df = 1 (P = 0.62), I^2 = 0$
Test for overall effect: $Z = 1.50 (P = 0.12)$

Fig. 2a

| Study or Subgroup | Disease Group Events | Control Group Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
|-------------------|----------------------|----------------------|-------|--------|---------------------|---------------------|
| Cong 2010         | 0                    | 140                  | 1     | 254    | 27.8%               | 0.60 [0.02, 14.86] |
| Eser 2010         | 2                    | 300                  | 0     | 300    | 12.9%               | 5.03 [0.24, 105.29] |
| Horton (Hand) 1998| 0                    | 86                   | 1     | 100    | 35.9%               | 0.36 [0.02, 9.53]   |
| Horton (Knee) 1998| 0                    | 56                   | 1     | 130    | 23.5%               | 0.76 [0.03, 19.04]  |
| Kawaguchi 1999    | 0                    | 64                   | 0     | 64     | Not estimable       | Not estimable       |
| Kim 2011          | 0                    | 86                   | 0     | 24     | Not estimable       | Not estimable       |
| Solovieva 2007    | 0                    | 232                  | 0     | 32     | Not estimable       | Not estimable       |

Total (95% CI): 964
Total events: 2
Heterogeneity: $\chi^2 = 1.57, df = 3 (P = 0.67), I^2 = 0$
Test for overall effect: $Z = 0.18 (P = 0.86)$

Fig. 2b

| Study or Subgroup | Disease Group Events | Control Group Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
|-------------------|----------------------|----------------------|-------|--------|---------------------|---------------------|
| Cong 2010         | 8                    | 140                  | 1     | 254    | 12.1%               | 15.33 [1.90, 123.90]|
| Eser 2010         | 13                   | 300                  | 2     | 300    | 34.6%               | 6.78 [1.51, 30.17]  |
| Horton (Hand) 1998| 0                    | 86                   | 0     | 150    | Not estimable       | Not estimable       |
| Horton (Knee) 1998| 0                    | 56                   | 0     | 130    | Not estimable       | Not estimable       |
| Kawaguchi 1999    | 3                    | 64                   | 0     | 64     | 8.6%                | 7.34 [0.37, 145.07] |
| Kim 2011          | 5                    | 86                   | 0     | 24     | 13.2%               | 3.21 [0.18, 61.93]  |
| Solovieva 2007    | 2                    | 232                  | 1     | 32     | 31.5%               | 0.27 [0.02, 3.06]   |

Total (95% CI): 964
Total events: 31
Heterogeneity: $\chi^2 = 7.02, df = 4 (P = 0.13), I^2 = 43$
Test for overall effect: $Z = 3.52 (P = 0.0004)$

Fig. 2c

| Study or Subgroup | Disease Group Events | Control Group Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
|-------------------|----------------------|----------------------|-------|--------|---------------------|---------------------|
| Cong 2010         | 4                    | 140                  | 10    | 254    | 18.2%               | 0.72 [0.22, 2.33]   |
| Eser 2010         | 26                   | 300                  | 24    | 300    | 57.8%               | 1.09 [0.81, 1.45]   |
| Horton (Hand) 1998| 1                    | 86                   | 3     | 100    | 7.2%                | 0.38 [0.04, 3.73]   |
| Horton (Knee) 1998| 1                    | 56                   | 3     | 130    | 4.7%                | 0.77 [0.08, 7.56]   |
| Kawaguchi 1999    | 1                    | 64                   | 3     | 64     | 7.8%                | 0.32 [0.03, 3.19]   |
| Kim 2011          | 4                    | 86                   | 0     | 24     | 15.9%               | 2.07 [0.14, 31.39]  |
| Solovieva 2007    | 2                    | 232                  | 0     | 32     | 23.3%               | 0.70 [0.03, 15.01]  |

Total (95% CI): 964
Total events: 39
Heterogeneity: $\chi^2 = 2.44, df = 6 (P = 0.88), I^2 = 0$
Test for overall effect: $Z = 0.36 (P = 0.72)$

Fig. 2d

| Study or Subgroup | Disease Group Events | Control Group Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
|-------------------|----------------------|----------------------|-------|--------|---------------------|---------------------|
| Cong 2010         | 8                    | 140                  | 14    | 254    | 86.0%               | 1.04 [0.42, 2.54]   |
| Eser 2010         | 0                    | 300                  | 0     | 300    | Not estimable       | Not estimable       |
| Horton (Hand) 1998| 0                    | 86                   | 0     | 100    | Not estimable       | Not estimable       |
| Horton (Knee) 1998| 0                    | 56                   | 0     | 130    | Not estimable       | Not estimable       |
| Kawaguchi 1999    | 0                    | 64                   | 0     | 64     | Not estimable       | Not estimable       |
| Kim 2011          | 2                    | 86                   | 1     | 24     | 14.0%               | 0.55 [0.05, 6.31]   |
| Solovieva 2007    | 0                    | 232                  | 0     | 32     | Not estimable       | Not estimable       |

Total (95% CI): 964
Total events: 10
Heterogeneity: $\chi^2 = 0.23, df = 1 (P = 0.63), I^2 = 0$
Test for overall effect: $Z = 0.07 (P = 0.94)$

Fig. 2e

(continued)
### Table 1: Distribution of Aggrecan Gene Vntr Polymorphism and Degenerative Disc Disease/Osteoarthritis

| Study or Subgroup | Disease Group | Control Group | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|---------------|---------------|-------------------------------|
| Cong 2010         | 14            | 140           | 0.80 [0.41, 1.56]             |
| Eser 2010         | 0             | 300           | Not estimable                 |
| Horton (Hand) 1998| 0             | 86            | Not estimable                 |
| Horton (Knee) 1998| 0             | 130           | Not estimable                 |
| Kawaguchi 1989    | 0             | 94            | Not estimable                 |
| Kim 2011          | 4             | 86            | 1.12 [0.12, 10.53]            |
| Solovieva 2007    | 1             | 232           | 0.42 [0.02, 10.56]            |
| **Total (95% CI)**| **964**       | **904**       | **0.81 [0.42, 1.51]**        |

### Figure 2f

![Graph](image)

### Table 2: Distribution of Aggrecan Gene Vntr Polymorphism and Degenerative Disc Disease/Osteoarthritis

| Study or Subgroup | Disease Group | Control Group | Odds Ratio M-H, Random, 95% CI |
|-------------------|---------------|---------------|-------------------------------|
| Cong 2010         | 33            | 140           | 2.22 [1.29, 3.81]             |
| Eser 2010         | 28            | 300           | 0.96 [0.56, 1.69]             |
| Horton (Hand) 1998| 3             | 69            | 1.17 [0.23, 0.99]             |
| Horton (Knee) 1998| 1             | 56            | 0.48 [0.05, 3.98]             |
| Kawaguchi 1999    | 6             | 64            | 3.21 [0.62, 16.53]            |
| Kim 2011          | 7             | 86            | 2.04 [0.24, 17.43]            |
| Solovieva 2007    | 42            | 232           | 0.49 [0.21, 1.10]             |
| **Total (95% CI)**| **964**       | **904**       | **1.18 [0.67, 2.09]**        |

### Figure 2g

![Graph](image)

### Table 3: Distribution of Aggrecan Gene Vntr Polymorphism and Degenerative Disc Disease/Osteoarthritis

| Study or Subgroup | Disease Group | Control Group | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|---------------|---------------|-------------------------------|
| Cong 2010         | 19            | 140           | 0.95 [0.52, 1.73]             |
| Eser 2010         | 43            | 300           | 0.56 [0.37, 0.85]             |
| Horton (Hand) 1998| 14            | 86            | 0.95 [0.44, 2.06]             |
| Horton (Knee) 1998| 12            | 56            | 1.59 [0.71, 3.56]             |
| Kawaguchi 1999    | 20            | 64            | 1.48 [0.68, 3.25]             |
| Kim 2011          | 21            | 86            | 1.23 [0.41, 3.69]             |
| Solovieva 2007    | 81            | 232           | 1.92 [0.79, 4.62]             |
| **Total (95% CI)**| **964**       | **904**       | **0.93 [0.73, 1.20]**        |

### Figure 2h

![Graph](image)

### Table 4: Distribution of Aggrecan Gene Vntr Polymorphism and Degenerative Disc Disease/Osteoarthritis

| Study or Subgroup | Disease Group | Control Group | Odds Ratio M-H, Random, 95% CI |
|-------------------|---------------|---------------|-------------------------------|
| Cong 2010         | 34            | 140           | 1.11 [0.68, 1.86]             |
| Eser 2010         | 90            | 300           | 1.31 [0.91, 1.88]             |
| Horton (Hand) 1998| 45            | 86            | 2.04 [1.13, 3.88]             |
| Horton (Knee) 1998| 26            | 56            | 1.10 [0.58, 2.17]             |
| Kamaline 2006     | 150           | 449           | 0.69 [0.33, 0.98]             |
| Kawaguchi 1999    | 25            | 64            | 0.53 [0.39, 1.07]             |
| Kim 2011          | 30            | 86            | 0.38 [0.15, 0.98]             |
| Solovieva 2007    | 74            | 232           | 0.68 [0.32, 1.48]             |
| **Total (95% CI)**| **1412**      | **1596**      | **0.91 [0.66, 1.27]**        |

### Figure 2i

![Graph](image)

### Table 5: Distribution of Aggrecan Gene Vntr Polymorphism and Degenerative Disc Disease/Osteoarthritis

| Study or Subgroup | Disease Group | Control Group | Odds Ratio M-H, Random, 95% CI |
|-------------------|---------------|---------------|-------------------------------|
| Cong 2010         | 14            | 140           | 0.83 [0.42, 1.62]             |
| Eser 2010         | 63            | 300           | 0.91 [0.62, 1.34]             |
| Horton (Hand) 1998| 21            | 86            | 0.53 [0.28, 1.00]             |
| Horton (Knee) 1998| 16            | 56            | 0.81 [0.41, 1.61]             |
| Kawaguchi 1999    | 6             | 64            | 1.00 [0.30, 3.38]             |
| Kim 2011          | 11            | 86            | 1.61 [0.33, 7.83]             |
| Solovieva 2007    | 25            | 232           | 3.91 [0.51, 29.87]            |
| **Total (95% CI)**| **964**       | **904**       | **0.86 [0.66, 1.11]**        |

### Figure 2j

![Graph](image)

(continued)
gene VNTR, which is why we have considered them both in this meta-analysis. The human aggrecan gene VNTR is unique among the species evaluated to date as human genes possess VNTR polymorphism on exon 12, which encodes the CS1 domain. Both DDD and OA are multi-stage processes, in which several environmental or genetic factors dominate each stage, and may be affected by the interaction of environmental and genetic events. Therefore, there may be a relationship between gene polymorphisms and intermediate phenotypes rather than the end stage of this process.

This study has systematically assessed the relationship between the aggrecan gene VNTR polymorphism and DDD and/or OA. Xu et al. previously reviewed the association between aggrecan gene/vitamin D receptor gene polymorphisms and intervertebral disc degeneration in 2012, and subsequently Gu et al. reviewed aggrecan VNTR and LDD in 2013. However, both studies confused the number of participants and alleles. Thus, the results of their research are unconvincing.

In this meta-analysis, seven studies looking at the distribution of aggrecan VNTR have been identified, which assessed a total of 2928 alleles on OA and/or DDD. After pooling the data from these seven studies, we found that A21 (containing 21 repeats) was over-represented and increased the risk of DDD, which is similar to the findings of previous research. The results suggest that human beings carrying the shorter aggrecan VNTR alleles would possess a lower number of CS chains or the special G3 domain of the aggrecan molecular structure, and this will lead to impaired function of aggrecan. The aggrecan protein core is adjusted with GAG chains, including domains of CS and KS. The polyelectrolyte nature of these GAG chains maintain the high osmotic pressure of aggrecan. Thus, it is suggested that the shorter GAG chains or the special G3 domain of aggrecan will lead to less water retention.

### Table 1

| Study or Subgroup | Disease Group | Events | Control Group | Odds Ratio | Weight |
|-------------------|---------------|--------|---------------|------------|--------|
| Cong 2010         | 3             | 140    | 20            |            |        |
| Eser 2010         | 30            | 300    | 33            |            |        |
| Horton (Hand) 1998| 2             | 89     | 2             |            |        |
| Horton (Knee) 1998| 1             | 86     | 3             |            |        |
| Kawaguchi 1999    | 2             | 64     | 3             |            |        |
| Kim 2011          | 0             | 86     | 0             |            |        |
| Solovieva 2007    | 3             | 232    | 0             |            |        |
| Total (95% CI)    | 964           | 964    | 100.0%        |            |        |
| Total events      | 41            | 61     |               |            |        |

Heterogeneity: Chi² = 3.69, df = 5 (P = 0.59); P = 0%
Test for overall effect: Z = 1.53 (P = 0.12)

### Figures

**Fig. 2A**

Forest plots of aggrecan variable number of tandem repeats (VNTR) associated with degenerative disc disease and/or osteoarthritis in overall populations: a) A18, b) A19, c) A21, d) A22, e) A23, f) A24, g) A25, h) A26, i) A27, j) A28, k) A29, l) A32, and m) A33. The squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (CI). The area of the squares reflects the study-specific weight (inverse of the variance). Diamonds represent the pooled OR and 95% CI. M-H, Mantel–Haenszel method.
because of the contributions of other associated genes, it is still unclear whether this is there does appear to be an influence of aggrecan vNTR the prognosis of the clinical treatments.8,31

advised on how their lifestyle might affect potential devel-

could be applied to patients at risk. The patients could be between aggrecan gene vNTR and DDD and/or OA, and which treatments would be most useful.

DDD or oA disease, or situation, and to anticipate better

difficulties underlying a patient’s health, and for patient quality of life. High-level screening also provides doctors with the tools to comprehend fully the complicated mechanisms underlying a patient’s health, DDD or OA disease, or situation, and to anticipate better which treatments would be most useful.

This study systematically reviewed the relationship between aggrecan gene VNTR and DDD and/or OA, and could be applied to patients at risk. The patients could be advised on how their lifestyle might affect potential development of DDD and/or OA. Moreover, patients could be provided with further clinical direction on whether they will benefit from surgical treatments. Screening will also give DDD and OA patients the opportunity to evaluate the prognosis of the clinical treatments.8,31

Meta-analysis is a statistical method which uses pooled data from multiple surveys and research on the same problem in order to reach a more scientific and impartial conclusion. Ideally, a meta-analysis will include only studies that have a similar validated design, and contain large populations.12 The major strength of this systematic review is that we conducted a comprehensive search of multiple databases, selected and appraised studies by independent pairs of reviewers, and followed an a priori planned protocol that included several hypotheses for the role of aggrecan VNTR in DDD and/or OA. When drawing conclusions regarding the role of aggrecan VNTR in DDD/OA, we should consider several limitations of this meta-analysis. First, the number of included studies was comparatively small; only seven studies were evaluated. This limited our ability to perform the asymmetry test with the Stata software and produce a funnel plot to assess potential publication bias visually. Thus, we cannot identify unpublished research with negative results. The potential publication bias could lead to an overestimation of the association between aggrecan VNTR and DDD and/or OA.

In conclusion, this study demonstrates that the most frequent allele in all of the studies was A27. Comprehensive analysis of all seven selected studies revealed a relationship between aggrecan VNTR and DDD, which identifies that A21 may have an association with DDD. However, such an association may not be statistically significant for OA.

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Funding Statement
This study was supported by the Doctor Research Startup Fund of liaoning Province (201601114). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions
L. Cong: Analysis and interpretation of the data, Drafting of the article.
G. Tu: Conception and design of study.
D. Liang: Conception and design, Collection and assembly of data.

Conflicts of Interest Statement
None declared

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