Vitamin D Receptor Gene and Aggrecan Gene Polymorphisms and the Risk of Intervertebral Disc Degeneration — A Meta-Analysis

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Abstract

**Background:** A series of studies have been conducted to evaluate the associations between vitamin D receptor (VDR) and aggrecan variable numbers of tandem repeat (VNTR) polymorphisms and the risk of intervertebral disc degeneration (IDD), but produced conflicting results.

**Objective:** we performed a meta-analysis to address a more accurate estimation of the associations between the above gene polymorphisms and the risk of IDD.

**Methods:** A comprehensive literature search was conducted to identify all the relevant studies. The fixed or random effect model was selected based on the heterogeneity test among studies evaluated using the I². Publication bias was estimated using Begg’s funnel plots and Egger’s regression test.

**Results:** A total of 9, 5, 3, and 7 studies were finally included in the analyses for the associations between the VDR TaqI (rs731236), FokI (rs2228570), ApaI (rs7975232), or aggrecan VNTR polymorphisms and the risk of IDD, respectively. The combined results showed that none of the VDR (TaqI, FokI, ApaI) polymorphisms were significantly associated with the risk of IDD. In contrast, the alleles with shorter VNTR length was found to significantly increase the risk of IDD (25 vs. >25: OR = 1.850, 95% CI 1.477–2.318; 23 vs. >23: OR = 1.955, 95% CI 1.41–2.703). Subgroup analysis confirmed the above results. After excluding studies deviated from Hardy-Weinberg equilibrium (HWE) in controls, no other studies were found to significantly influence the pooled effects in each genetic model. No potential publication bias was detected.

**Conclusion:** This meta-analysis suggested that the alleles with shorter VNTR length significantly increased the risk of IDD, while the VDR (TaqI, FokI, ApaI) gene polymorphisms were not significantly associated with the risk of IDD. Since potential confounders could not be ruled out completely, further studies are needed to confirm these results.

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Introduction

Intervertebral disc degeneration (IDD) is a major pathological process implicated in low back pain, and is a prerequisite to disk herniation [1]. IDD has been attributed to the accumulation of environmental factors, primarily mechanical insults and injuries, imposed on the “normal” aging changes [2]. However, epidemiological studies on families and twins have suggested that inheritance may be the major determinant of IDD [3–5]. So far, several gene polymorphisms have been demonstrated to be associated with the risks of IDD [6].

Vitamin D receptor (VDR) gene is the first reported gene potentially associated with IDD risks [7]. VDR gene is located on human chromosome 12 (12q12–q14), with a length of 100 kb, and has more than 100 restriction endonuclease cutting site polymorphisms [8]. VDR is a member of the steroid superfamily of nuclear receptor, which plays a key role in the regulation of the transcriptional activity of vitamin D metabolite, 1α, 25-dihydroxyvitamin D3 [9]. VDR gene polymorphisms are thought to contribute to a variety of disorders including osteoporosis, osteoarthritis, tumor, and cardiovascular diseases [6]. In the past decades, there has been increasing interest in the study of the association between VDR gene polymorphisms and the risk of IDD. These studies have mostly focused on a few selected variants, including the TaqI (rs731236), FokI (rs2228570), and ApaI (rs7975232) restriction sites. However, the results have been inconsistent. Some studies suggested that VDR TaqI gene polymorphism was associated with increased risk of IDD [10–
Inclusion Criteria

Literature and Search Strategy

Materials and Methods

1. Inclusion Criteria

2. Statistical Analysis

3. Results

4. Discussion

5. Conclusion

6. Acknowledgments

7. References
associations existed in Caucasians (OR = 0.982, 95%CI 0.769–1.255) or Asians (OR = 1.137, 95%CI 0.599–2.158), in subjects with age >40 (OR = 1.161, 95%CI 0.773–1.742), or ≤40 (OR = 0.928, 95%CI 0.546–1.576), and in women (OR = 0.787, 95%CI 0.505–1.228) or men (OR = 1.172, 95%CI 0.715–1.918). No significant associations were found in genotype contrasts (tt/Tt vs. TT: OR = 0.991, 95%CI 0.617–1.591), and the subgroup analysis further confirmed the irrelevance between the genotypes and the risk of IDD. The results were not altered after excluding the studies by Chen et al., in which the 95%CI did not overlap the lines of the pooling results, a significant association was found in Asians (t vs. T: OR = 1.568, 95%CI 1.108–2.219).

The pooled results on the associations between VDR (FokI and ApaI) polymorphisms and the risks of IDD were similar to those of VDR TaqI and IDD risk. Overall, no significant association was found between VDR FokI polymorphism and IDD risk (f vs. F: OR = 0.929, 95%CI 0.779–1.109; ff vs. FF: OR = 1.146, 95%CI 0.719–1.826; Ff/ff vs. FF: OR = 1.012, 95%CI 0.621–1.649). Similarly, no significant association was found between VDR ApaI polymorphism and IDD risk (a vs. A: OR = 0.914, 95%CI 0.649–1.288; aa vs. AA; OR = 0.757, 95%CI 0.477–1.202; aa vs. Aa/AA: OR = 0.924, 95%CI 0.516–1.653). As limited studies were included for the above two association investigation, we did not perform subgroup analysis.

Results of pooled analysis on the associations between aggrecan VNTR polymorphism and the risk of IDD are shown in Table 4. In contrast to the null association between VDR polymorphisms and the risk of IDD, a significant association was observed.
between aggrecan VNTR polymorphism and the risk of IDD. The alleles with shorter VNTR length was found to significantly increase the risk of IDD (25 vs. 23: OR = 1.850, 95%CI 1.477–2.318; 23 vs. 22: OR = 1.955, 95%CI 1.41–2.703) (Fig. 3).

Significant association was also observed in Caucasians (25 vs. 23: OR = 2.006, 95%CI 1.468–2.450; 23 vs. 22: OR = 2.917, 95%CI 1.450–3.329) as well as in Asians (25 vs. 23: OR = 1.887, 95%CI 1.298–2.744; 23 vs. 22: OR = 1.618, 95%CI 0.960–2.727). Subgroup analysis stratified by gender and age also confirmed the above results.

Influence Analysis and Cumulative Analysis

After excluding studies that deviated from HWE in controls, and those in which 95%CI did not overlap the lines of the pooling

Table 1. Characteristics of individual studies for associations between VDR polymorphisms and IDD risks.

| Authors       | Year | Country | Ethnicity | Gender | Age (Year) | Genotypes distribution | $P_{hwe}$ |
|---------------|------|---------|-----------|--------|------------|------------------------|----------|
| TaqI (rs731236) |      |         |           |        |            |                        |          |
| Chen          | 2012 | China   | Asian     | Both   | 40.3       | 11 12 22              | 0.617    |
| Eskola        | 2010 | Danmark | Caucasian | Both   | 13.1       | 11 12 22              | 0.898    |
| Yuan          | 2010 | China   | Asian     | Both   | 43.63      | 11 12 22              | 0.382    |
| Eser          | 2010 | Turkey  | Caucasian | NA     | 20–30      | 0 14 86               |          |
| Cheung        | 2006 | China   | Asian     | Both   | 18–55      | 0 14 86               |          |
| Noponen-Hietala | 2003 | Filand | Caucasian | Both   | 48.5       | 0 14 86               | 0.768    |
| Oishi         | 2003 | Japan   | Asian     | Women  | 73.2       | 0 14 86               | 0.536    |
| Jones         | 1998 | Australia | Caucasian | Both   | 69.5       | 0 14 86               |          |
| FokI (rs2228570) |      |         |           |        |            |                        |          |
| Kelempisioti  | 2011 | Filand  | Caucasian | Both   | 40.3       | 0 14 86               | 0.032    |
| Eskola        | 2010 | Danmark | Caucasian | Both   | 13.1       | 0 14 86               | 0.898    |
| Eser          | 2010 | Turkey  | Caucasian | NA     | 20–30      | 0 14 86               |          |
| Chen          | 2007 | China   | Asian     | Both   | 40.3       | 0 14 86               | 0.883    |
| Noponen-Hietala | 2003 | Filand | Caucasian | Both   | 48.5       | 0 14 86               | 0.630    |
| ApaI (rs7975232) |      |         |           |        |            |                        |          |
| Chen          | 2012 | China   | Asian     | Both   | 40.3       | 0 14 86               | 0.945    |
| Yuan          | 2010 | China   | Asian     | Both   | 43.6       | 0 14 86               | 0.500    |
| Kawaguchi     | 2002 | Japan   | Asian     | Both   | 22         | 0 14 86               | 0.951    |

Table 2. Characteristics of individual studies for association between aggrecan VNTR polymorphism and IDD risk.

| Authors       | Year | Country | Ethnicity | Gender | Age (Year) | Alleles (most common one) | Case alleles$^a$ | Control alleles$^a$ |
|---------------|------|---------|-----------|--------|------------|--------------------------|-----------------|-------------------|
| Kim           | 2011 | Korea   | Asian     | Both   | <40        | 21;22;23;24;25;26;27;28;33;36 (27) | 22 64 3 21       |
| Eser          | 2011 | Turkey  | Caucasian | Both   | 22.3 (20–30) | 13;21;22;25;26;27;28;29;32 (28) | 27 73 19 81     |
| Mashayekhi    | 2010 | Iran    | Caucasian | Both   | 36(28–52)  | 21;19;21;22;23;24;25;26;27;28;29;32 (27) | 27 73 19 81     |
| Eser          | 2010 | Turkey  | Caucasian | Men    | 20–30      | 13;19;21;22;25;26;27;28;32;33 (27) | 33 38 20 88     |
| Cong          | 2010 | China   | Asian     | Men    | 36.0(14–49)| 18;19;20;21;22;23;24;25;26;27;28;29;30;31;32;33 (27) | 73 227 55 245   |
| Solovieva     | 2007 | Filand  | Caucasian | Men    | 44(41–46)  | 21;22;24;25;26;27;28;29;32 (26) | 11 19 47 185    |
| Kawaguchi     | 1999 | Japan   | Asian     | Women  | 21.3 (20–29)| 18;21;22;25;26;27;28;29 (27) | 11 53 5 9       |

*the mean age and/or the range of age;
$^a$the variable numbers of tandem repeat(VNTR) alleles detected, and the most common form.
$^b$the VNTR numbers.

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results, no other studies were found to significantly influence the pooled effects in each genetic model. In the cumulative meta-analysis, no particular time trend was found in the summary estimate.

Publication Bias

Funnel plots were generated to assess publication bias. The Egger’s test was performed to statistically evaluate funnel plot symmetry. The results suggested no publication bias for the association of the VDR (TaqI, FokI, or ApaI) and aggrecan VNTR polymorphisms and the risk of IDD (P_Egger test = 0.718, 0.128, 0.341, and 0.181, respectively) (Fig. 4).

Discussion

IDD was traditionally regarded as a result of mechanical overloading and senescence; however, recent studies have showed that genetic factors may play a crucial role [35]. In the past few decades, many gene polymorphisms including collagen, interleukins, matrix degrading enzymes, VDR, and aggrecan, have been shown to be related with the risks of IDD [6]. VDR is the firstly reported gene associated with IDD risk in a study of monozygotic twins in Finns with FokI and TaqI genotypes [7], while aggrecan VNTR polymorphism is a recently widely studied polymorphism for the risk of IDD. Unfortunately, conflicting results are obtained ranging from strong links to no association. The divergent results regarding the effects of these genetic polymorphisms upon IDD risk may be attributed to the differences in racial origin of the population, the age, and the occupation of the subjects. Because of the above-mentioned conflicting results from relatively small studies underpowered to detect the effects, a meta-analysis should be an appropriate approach to obtain a more definitive conclusion.

To the best of our knowledge, this is the first meta-analysis addressing the associations between VDR (TaqI, FokI, ApaI) and aggrecan VNTR polymorphisms and the risks of IDD. In this study, a total of 9, 5, 3, and 7 studies were finally included in the analyses for the association between the VDR TaqI, FokI, ApaI or aggrecan VNTR polymorphisms and the risks of IDD, respectively. The combined results showed that none of the three VDR polymorphisms were significantly associated with the IDD risk. Subgroup analysis stratified by ethnicity, age, and sex, also revealed no association, although a significant association was found in Asians (t vs. T: OR = 1.568, 95% CI 1.108–2.219) when excluding one study, in which the 95% CI did not overlap the lines of the pooling results. In contrast, aggrecan VNTR polymorphism was found to be significantly associated with the risk of IDD. The alleles of shorter VNTR length was found to significantly increase the risk of IDD (t vs. T: OR = 1.568, 95% CI 1.108–2.219; 25 vs. >25: OR = 1.850, 95% CI 1.477–2.318; 23 vs. >23: OR = 1.955, 95% CI 1.41–2.703). Subgroup analysis stratified by ethnicity, gender and age also confirmed the above results. After excluding studies that deviated from HWE in controls, no other studies were found to significantly influence the pooled effects in each genetic model. Cumulative meta-analysis showed that no particular time trend existed in the summary estimate. Furthermore, no potential publication bias was detected by funnel plots and Egger’s regression test. These data indicated the robustness of the summary estimate derived from this study.

Aggrecan is the major proteoglycan of the disk, which is responsible for maintaining tissue hydration through the osmotic...
pressure provided by its constituent chondroitin (CS) and keratin sulfate chains (KS) [37]. The human aggrecan gene possesses a variable number tandem repeat, VNTR, polymorphism in the part of exon 12 encoding the CS1 domain [15]. Alleles have been identified with CS1 repeat numbers ranging from 13 to 33, with the most common alleles containing 26, 27, or 28 repeats [19]. It appears logically that individuals possessing the shortest VNTR numbers have the lowest number of CS chains on their aggrecan molecules, and this configuration may result in impaired aggrecan function. Although the association between aggrecan VNTR polymorphism and risk of IDD was not found in some studies [20], this meta-analysis provided strong evidence for the above association. The alleles with shorter VNTR repeats were overexpressed in IDD patient than control subjects. As no studies provided the genotypes of each participant, thus we did not compare the distribution of genotypes between case and control groups.

VDR is a steroid nuclear receptor, better known to have an important role in normal bone mineralization and remodeling. VDR expression was reported in chondrocytes and is thought to be involved in differentiation, proliferation, and maturation of cartilage [38]. In addition, vitamin D has been shown to influence proteoglycan synthesis [39]. Polymorphisms in VDR gene could influence the stability of the mRNA and vitamin D expression [10]. Although several studies have shown that VDR polymorphisms were associated with the risks of IDD, the current meta-analysis did not find any significant association between the three polymorphisms, FokI (rs2228570), TaqI (rs731236), and ApaI (rs7975232), and the IDD risks. However, after scrutiny of the included studies, we could find that most of the studies included for the analysis of VDR gene polymorphisms. Therefore, it could be speculated that the potential association between VDR polymorphisms and IDD may be obscured by some environmental factors. Furthermore, VDR polymorphisms have been reported to be significantly associated with the multilevel and severe forms of IDD [11,31]. Thus, the associations between VDR gene polymorphisms and the risks of IDD could not be excluded.

Despite the clear strengths of our study such as the larger sample size comparing with the previous individual ones, it does have some limitations. First, the present meta-analysis was based primarily on unadjusted effect estimates and CIs (since most studies did not provide the adjusted OR and 95%CI controlling for potential confounding factors), thus the effect estimates were relatively imprecise. If individual data were available, adjusted ORs could be obtained to give a more precise analysis. Second, it

| Sub-group | Test of association | Test of heterogeneity |
|-----------|---------------------|-----------------------|
|           | OR  | 95%CI  | Statistical model | I² (%) | p value |
| TaqI      |     |        |                  |        |         |
| f vs. T   | 0.982 | 0.769–1.255 | FEM | 0.0 | 0.649 |
| Asian     | 1.137 | 0.599–2.158 | REM | 66.2 | 0.019 |
| >40       | 1.161 | 0.773–1.742 | FEM | 0.0 | 0.830 |
| ≤40       | 0.928 | 0.546–1.576 | REM | 72.3 | 0.013 |
| Women     | 0.787 | 0.505–1.228 | FEM | 0.0 | 0.549 |
| men       | 1.172 | 0.715–1.918 | FEM | 0.0 | 0.829 |
| Both      | 1.160 | 0.688–1.954 | REM | 68.0 | 0.014 |
| all       | 1.109 | 0.803–1.533 | REM | 52.8 | 0.038 |
| Ti/tt vs. TT |     |        |                  |        |         |
| Caucasian | 0.754 | 0.489–1.162 | FEM | 7.4 | 0.340 |
| Asian     | 1.158 | 0.595–2.253 | REM | 66.0 | 0.019 |
| >40       | 1.003 | 0.685–1.470 | FEM | 0.0 | 0.448 |
| ≤40       | 1.135 | 0.375–3.431 | REM | 83.7 | 0.000 |
| Women     | 0.770 | 0.453–1.309 | FEM | 0.0 | 0.424 |
| men       | 1.211 | 0.658–2.226 | FEM | 0.0 | 0.849 |
| Both      | 0.949 | 0.424–2.124 | REM | 75.3 | 0.003 |
| all       | 0.991 | 0.617–1.591 | REM | 62.2 | 0.010 |
| FokI      |     |        |                  |        |         |
| f vs. F   | 0.929 | 0.779–1.109 | FEM | 25.7 | 0.250 |
| ff vs. FF | 1.146 | 0.719–1.826 | FEM | 0.0 | 0.467 |
| Ff/ff vs. FF | 1.012 | 0.621–1.649 | REM | 60.7 | 0.054 |
| ApaI      |     |        |                  |        |         |
| a vs. A   | 0.914 | 0.649–1.288 | REM | 60.1 | 0.082 |
| aa vs. AA | 0.757 | 0.477–1.202 | FEM | 0.0 | 0.379 |
| aa vs. AA/Aa | 0.924 | 0.516–1.653 | REM | 74.7 | 0.019 |

*p value for heterogeneity based on Q test; FEM, fixed effect model. REM, random effect model.

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Figure 3. Meta-analysis for aggrecan VNTR polymorphism and the risk of IDD (≤25 vs. >25). Each study was shown by a point estimate of the effect size (OR) (size inversely proportional to its variance) and its 95% confidence interval (95%CI) (horizontal lines). The white diamond denotes the pooled OR.

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Table 4. Summary of ORs for various genetic contrasts on the association between aggrecan VNTR polymorphism and IDD risk.

| Sub-group | No. of studies | Test of association | Test of heterogeneity |
|-----------|----------------|---------------------|-----------------------|
| ≤25 vs. >25 |                 |                     |                       |
| Caucasian | 4              | 2.006, 1.468–2.450  | 0.003, REM, 54.2%     |
| Asian     | 3              | 1.887, 1.298–2.744  | 0.001, fixed effect, 0.0% |
| >30       | 3              | 2.199, 1.591–3.040  | 0.000, fixed effect, 45.6% |
| ≤10       | 3              | 1.537, 1.112–2.124  | 0.009, fixed effect, 0.0% |
| Women     | 1              | 2.449, 0.799–7.508  | 0.117, fixed effect, — |
| men       | 3              | 1.636, 1.248–2.145  | 0.000, fixed effect, 0.0% |
| Both      | 3              | 2.426, 1.558–3.778  | 0.000, fixed effect, 40.4% |
| All       | 7              | 1.850, 1.477–2.318  | 0.000, fixed effect, 14.4% |
| ≥23 vs. >23 |               |                     |                       |
| Caucasian | 3              | 2.197, 1.450–3.329  | 0.000, fixed effect, 0.0% |
| Asian     | 3              | 1.618, 0.960–2.727  | 0.071, fixed effect, 0.0% |
| >30       | 3              | 1.986, 1.271–3.103  | 0.003, fixed effect, 23.3% |
| ≤10       | 2              | 1.845, 1.137–2.992  | 0.013, fixed effect, 0.0% |
| Women     | 1              | 1.723, 0.394–7.535  | 0.470, fixed effect, — |
| men       | 3              | 1.691, 1.157–2.471  | 0.007, fixed effect, 0.0% |
| Both      | 2              | 3.241, 1.590–6.606  | 0.001, fixed effect, 0.0% |
| All       | 6              | 1.955, 1.414–2.703  | 0.000, fixed effect, 0.0% |

*p value for heterogeneity based on Q test; FEM, fixed effect model. REM, random effect model.

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has been well known that IDD is a multifactor disease, however, the effects of gene-gene and gene-environment interactions were not addressed in this meta-analysis, and thus the potential roles of the above gene polymorphisms may be masked or magnified by other gene-gene/gene-environment interactions. Thirdly, although the funnel plot and Egger’s test showed no publication bias, selection bias may also exist because only published studies in English or Chinese were retrieved.

In summary, the current meta-analysis systematically analyzed the associations between VDR (TaqI, FokI, ApaI) and aggrecan VNTR polymorphisms and the risks of IDD. The combined results clearly showed that the alleles with shorter VNTR length significantly increased the risk of IDD in Caucasians as well as in Asians. In contrast, none of the VDR (TaqI, FokI, ApaI) gene polymorphisms were significantly associated with the development of IDD. Since potential confounders could not be ruled out completely, further studies are needed to confirm these results.

Supporting Information

PRISMA Checklist S1  PRISMA Checklist.
(DOC)

Author Contributions

Conceived and designed the experiments: GX QM. Performed the experiments: QM DJZ JLW LH. Analyzed the data: QM DJZ JLW LH. Wrote the paper: GX QM LH.

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