



Relationship Between GDF5 +104T/C Polymorphism and the Susceptibility of Lumbar Disc Degeneration: A Meta-Analysis

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ABSTRACT

Lumbar disc degeneration (LDD) is a multifactorial and chronic disease with a complex genetic background. Previous studies have reported the strong association between growth differentiation factor 5 (GDF5) +104T/C polymorphism and the risk of LDD in different ethnic populations. The aim of this study was to analyze the association between the GDF5 +104T/C polymorphism and the susceptibility of LDD by a meta-analysis. Potentially relevant studies were selected by electronic databases (PubMed, EMBASE, Web of science, the Cochrane Library Chinese National Knowledge Infrastructure) up to 10th April 2017. Summary odds ratio (OR) and 95% confidence intervals (CIs) were used to assess the strength of association between the GDF5 +104T/C polymorphism and LDD risk. Six case-control studies, including 1107 LDD cases and 4353 controls, were included. The combined results showed that GDF5 +104T/C polymorphism was significantly associated with increased susceptibility to LDD at the allele level (T vs. C: OR = 1.52, 95%CI = 1.21-1.90) and genotype level (TT vs. CC: OR = 2.43, 95%CI = 1.81-3.25; TC vs. CC: OR = 1.84, 95%CI = 1.37-2.47; TT+TC vs. CC: OR = 2.14, 95%CI = 1.61-2.84; TT vs. TC+CC: OR = 1.42, 95%CI = 1.01-1.99) in the overall population. After stratified by ethnicity, we found a strong significant association (OR = 1.80 to 3.70, all $P < 0.05$) in Asian population and weaker associations (OR = 1.20 to 1.64, all $P < 0.05$) in Caucasian population. This meta-analysis suggests an increased risk of GDF5 +104T/C polymorphism against intervertebral disc degeneration among populations especially in Asians.

KEYWORDS: Lumbar disc degeneration; GDF5; rs143383; Polymorphism; Meta-analysis

ABBREVIATIONS: CI: Confidence Interval; GDF5: Growth Differentiation Factor 5; LDD: Lumbar Disk Degeneration; OR: Odds Ratio; HWE: Hardy-Weinberg's Equilibrium; SNP: Single Nucleotide Polymorphism

INTRODUCTION

Low back pain is one of the world's most frequent disorders, and 70–85% of all people have back pain at some point in their life. It is a major source affecting quality of life and has a substantial impact on the cost of health care, leading to a significant burden of social and economic worldwide [1,2]. Lumbar disc degeneration (LDD) is the major cause of low back pain [3,4]. Although the etiology and pathogenesis of LDD are still not fully elucidated, epidemiologic studies have suggested that LDD is associated with environmental factors such as body weight, mechanical loading, physical activities and smoking [5]. In addition, heritability studies have shown that

a series of genetic factors play important roles in the development of LDD [6-8]. One of the most comprehensively studied candidate genes is growth differentiation factor 5 (GDF5), a member of the transforming growth factor- β superfamily and closely correlated with bone morphogenetic proteins. Previous studies have demonstrated that GDF5 play an important role in musculoskeletal processes, affecting endochondral ossification, maintenance of tendon, formation of synovial joint and bone [9,10]. A single nucleotide polymorphism (SNP) (rs143383) involved in the regulation of GDF5 transcriptional activity has been identified

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in subjects carrying the T allele [11]. In the past several years, several reports have shown the association between GDF5 gene polymorphisms and the risk of osteoarthritis, congenital dysplasia of the hip. Recently, a number of research groups have reported the GDF5 +104T/C SNP is a protective factor for LDD [12-17].

A recent meta-analysis showed that there is an association between GDF5 (+104T/C) and lumbar disc degeneration in Northern European population, suggesting that GDF5 rs143383 polymorphism may be related to an elevated risk of LDD in a certain ethnic group[18]. However, these positive associations have not been analyzed in other ethnic groups. More recently, several new studies have also reported that the association of GDF5 +104T/C SNP in the promoter region might be a risk factor of LDD in Asian population.

Therefore, this study aimed to summarize the current data and update the meta-analysis, which may minimize potential publications bias, enlarge the sample size and provide more solid evidence. In the present study, a meta-analysis was performed to

assess the associations between GDF5 +104T/C polymorphism and the susceptibility of the LDD in different ethnic populations.

RESULTS

Study Characteristics

As shown in Figure 1, a total of 270 studies were obtained from databases after initial search, and three of them were selected from the reference lists of the identified publications. After first screening, 79 of them were excluded based on the selection criteria. And 172 of records were excluded for improper title/abstract. Among the remaining 19 studies, 3 were review studies; 5 reported other disease; 3 were not case-control studies and 2 were not about human. Finally, 6 eligible studies were included in this meta-analysis, including 1107 cases and 4353 controls. The detailed characteristics of the included articles are shown in Table 1. Genotype distributions among the controls of all included studies were corresponded to HWE. The 6 case-control studies were published between 1994 and 2014. Among them, 3 studies were conducted in Caucasian and 3 in Asian.

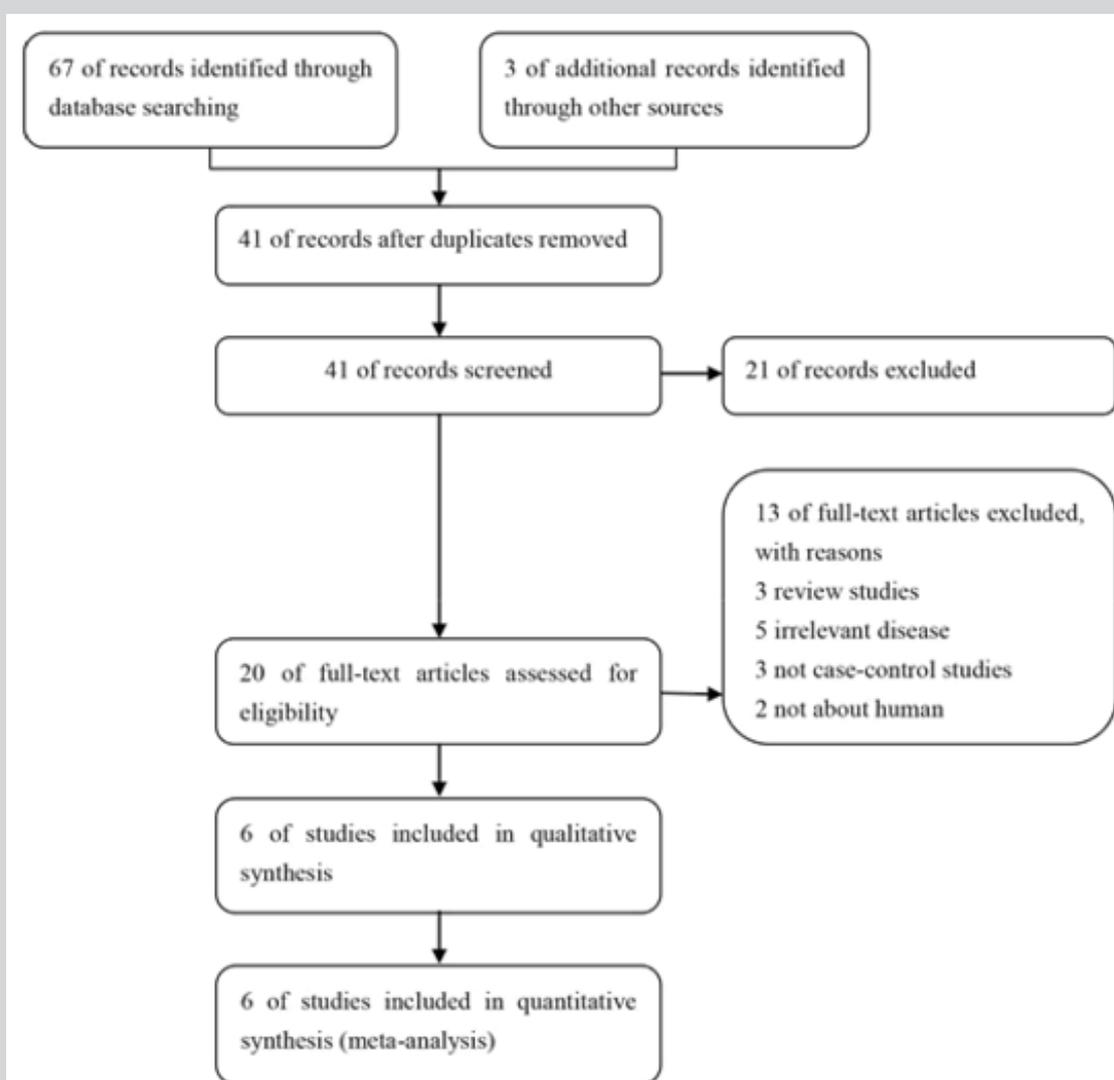


Figure 1: Flow diagram of the study selection process.

Table 1: Characteristics of studies included in the meta-analysis.

| Study | Country | Ethnicity | Study Design | Control Source | Genotype Distribution (case/control) | | | HWE (P) | Quality |
|----------------|---------|-----------|--------------|----------------|--------------------------------------|---------|--------|---------|---------|
| | | | | | TT | TC | CC | | |
| Spector et al. | Britain | Caucasi | Case-contro | Population | 9/246 | 7/256 | Feb-72 | 0.671 | ***** |
| Yuan et al. | Chines | Asian | Case-contro | Hospital | 206/275 | 89/254 | Oct-58 | 0.523 | ***** |
| Bijkerk et al. | Hollan | Caucasi | Case-contro | Population | 85/657 | 117/838 | 25/312 | 0.112 | ***** |
| Hart et al. | Britain | Caucasi | Case-contro | Population | 25/273 | 23/312 | 6/119 | 0.067 | ***** |
| Mu et al. | Chines | Asian | Case-contro | Hospital | 206/275 | 89/254 | Oct-58 | 0.954 | ***** |
| Mu et al. | Chines | Asian | Case-contro | Hospital | 144/173 | 79/158 | Aug-39 | 0.743 | ***** |

Abbreviations: Hardy-Weinberg's equilibrium

Meta-Analysis Results

As shown in Table 2 and Figure 2, The association was found between the GDF5 +104T/C polymorphism and LDD susceptibility in all the genetic models: T vs. C (OR = 1.52, 95%CI = 1.21-1.90, $P < 0.001$), TT vs. CC (OR = 2.43, 95%CI = 1.81-3.25; $P < 0.001$), TC vs. CC (OR = 1.84, 95%CI = 1.37-2.47, $P < 0.001$), TT+TC vs. CC (OR = 2.14, 95%CI = 1.61-2.84, $P < 0.001$), TT vs. TC+CC (OR = 1.42, 95%CI = 1.01-1.99, $P = 0.04$) (Figure 2). In the subgroup analysis stratified by ethnicity, studies were divided into Caucasian and Asian populations. The same association was found in the Caucasian

(T vs. C: OR = 1.20, 95%CI = 1.01-1.43, $P = 0.04$; TT vs. CC: OR = 1.63, 95%CI = 1.09-2.44; $P = 0.02$; TC vs. CC: OR = 1.64, 95%CI = 1.11-2.42, $P = 0.01$; TT+TC vs. CC: OR = 1.64, 95%CI = 1.61-2.84, $P = 0.01$) and Asians (T vs. C: OR = 1.80, 95%CI = 1.55-2.09, $P < 0.001$; TT vs. CC: OR = 3.70, 95%CI = 2.39-5.71; $P < 0.001$; TC vs. CC: OR = 2.14, 95%CI = 1.37-3.34, $P < 0.001$; TT+TC vs. CC: OR = 2.98, 95%CI = 1.94-4.58, $P < 0.001$; TT vs. TC+CC: OR = 1.86, 95%CI = 1.39-2.50, $P < 0.001$) groups. But the GDF5 +104T/C polymorphism was not significantly associated with LDD in Caucasians when comparing TT vs. TC+CC genotypes (OR = 1.00, 95 % CI = 0.78-1.28, $P = 0.99$). (Figure 3); (Table. 2).

Table 2: Meta-analysis of the association of GDF5 (+104T/C) polymorphism with LDD risk.

| Comparisons | Stratifications | Test of Association | | | Test of Heterogeneity | | Effects Model |
|--------------|-----------------|---------------------|-----------|-----------|-----------------------|---------|---------------|
| | | OR | 95%CI | P-Value | I ² (%) | P-Value | |
| T vs. C | Overall | 1.52 | 1.21-1.90 | 0.0003 | 69% | 0.006 | Random |
| | Caucasian | 1.2 | 1.01-1.43 | 0.04 | 0% | 0.85 | Fixed |
| | Asian | 1.8 | 1.55-2.09 | < 0.00001 | 55% | 0.11 | Random |
| TT vs. CC | Overall | 2.43 | 1.81-3.25 | < 0.00001 | 39% | 0.14 | Fixed |
| | Caucasian | 1.63 | 1.09-2.44 | 0.02 | 0% | 0.94 | Fixed |
| | Asian | 3.7 | 2.39-5.71 | < 0.00001 | 0% | 0.59 | Fixed |
| TC vs. CC | Overall | 1.84 | 1.37-2.47 | < 0.0001 | 0% | 0.92 | Fixed |
| | Caucasian | 1.64 | 1.11-2.42 | 0.01 | 0% | 0.77 | Fixed |
| | Asian | 2.14 | 1.37-3.34 | 0.0009 | 0% | 0.93 | Fixed |
| TT+TC vs. CC | Overall | 2.14 | 1.61-2.84 | < 0.00001 | 0% | 0.44 | Fixed |
| | Caucasian | 1.64 | 1.13-2.38 | 0.01 | 0% | 0.89 | Fixed |
| | Asian | 2.98 | 1.94-4.58 | < 0.00001 | 0% | 0.79 | Fixed |
| TT vs. TC+CC | Overall | 1.42 | 1.01-1.99 | 0.04 | 78% | 0.0003 | Random |
| | Caucasian | 1 | 0.78-1.28 | 0.99 | 0% | 0.51 | Fixed |
| | Asian | 1.86 | 1.39-2.50 | < 0.0001 | 61% | 0.08 | Random |

Abbreviations: LDD: Lumbar Disc Degeneration; CI: Confidence Interval; OR: Odds Ratio

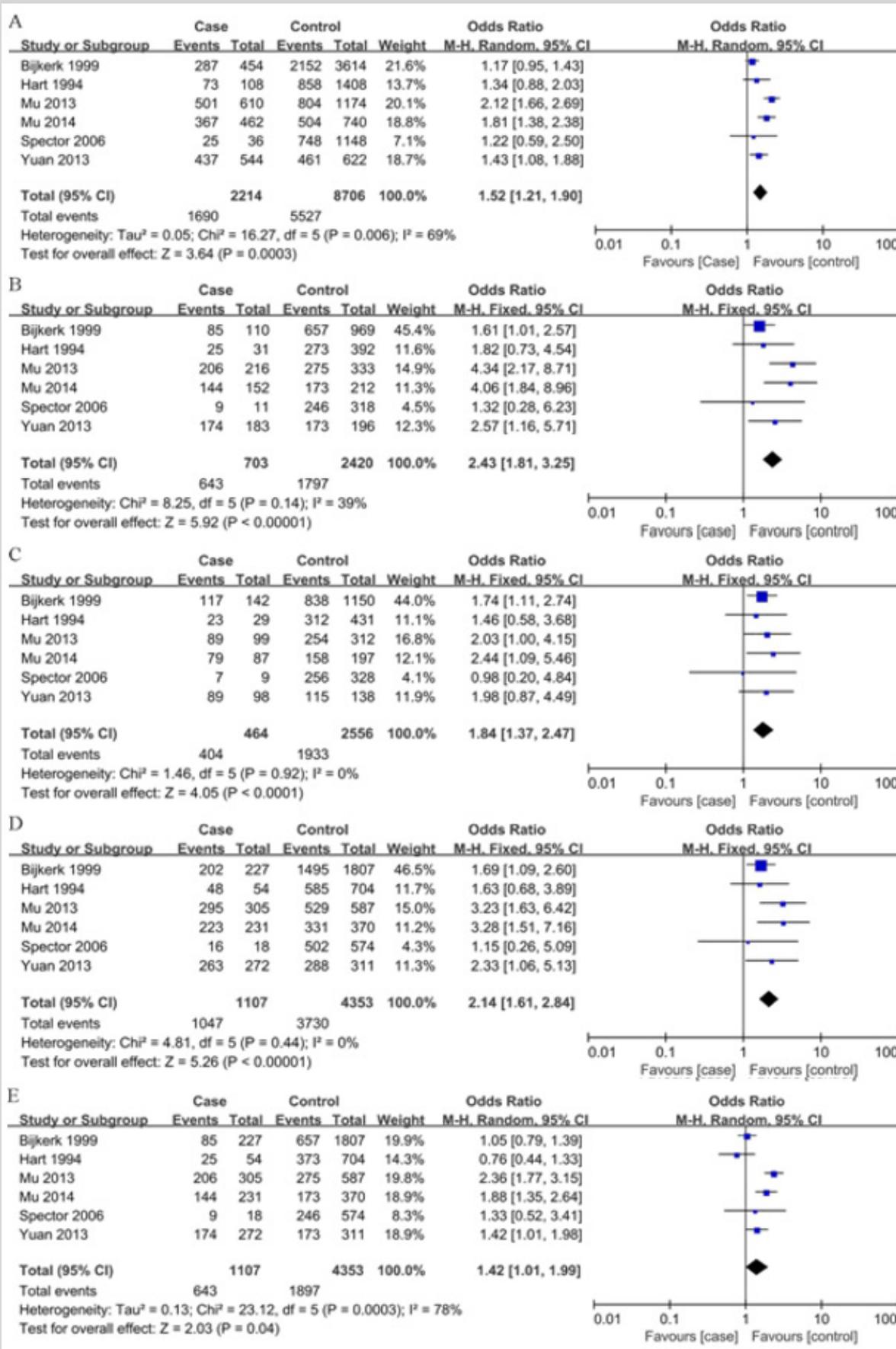


Figure 2: Forest plots for association between GDF5 +104T/C polymorphism and LDD risk in different genetic models. ((A) Allele model (T vs. C); (B) Homozygote model (TT vs. CC); (C) Heterozygote model (TC vs. CC); (D) Dominant mode (TT+TC vs. CC); (E) Recessive model (TT vs. TC+CC)).

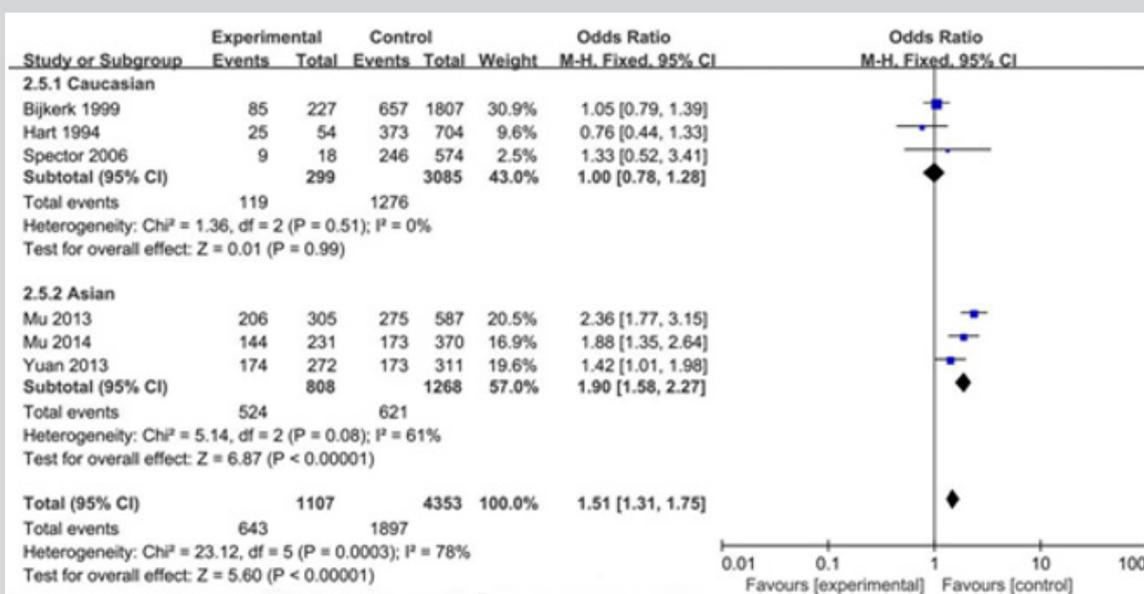


Figure 3: Forest plots for association between GDF5 +104T/C polymorphism and LDD risk based on ethnicity. ((A) Allele model (T vs. C); (B) Homozygote model (TT vs. CC); (C) Heterozygote model (TC vs. CC); (D) Dominant model (TT+TC vs. CC); (E) Recessive model (TT vs. TC+CC)).

Heterogeneity Analysis

In Q test, significant heterogeneity was detected in allele T vs. allele C model ($P=0.006$) and TT vs. TC+CC model ($P=0.0003$). Therefore, the random-effects model was used to evaluate overall results in these two models, while the fixed-effects model was selected for the other three models (TT vs. CC: $P = 0.14$; TC vs. CC: $P=0.92$; TT+TC vs. CC: $P=0.44$). Notably, the significant heterogeneity of that two models was considerably decreased after subgroup analysis by ethnicity, which might contribute to the heterogeneity.

Sensitivity Analysis

We removed one single study from the overall pooled analysis each time and recalculated overall outcomes to evaluate the impact of each included study on pooled results. The pooled ORs were not substantially changed, suggesting that our results were statistically stable and reliable.

Publication Bias

Both Begg’s test and Egger’s test were used to evaluate the possibility of existing significant publication bias. No significant publication bias was found in the Begg’s test and Egger’s test ($P>0.05$) (Table 3).

Table 3: Publication bias tests for association between GDF5 +104T/C polymorphism and LDD.

| Comparisons | Egger Test | Begg Test | P-Value |
|--------------|------------|-----------------|---------|
| | P-Value | 95%CI | |
| T vs. C | 0.975 | (-7.070, 6.901) | 0.452 |
| TT vs. CC | 0.994 | (-2.515, 2.500) | 0.452 |
| TC vs. CC | 0.571 | (-2.320, 1.477) | 0.26 |
| TT+TC vs. CC | 0.836 | (-3.340, 3.918) | 0.452 |
| TT vs. TC+CC | 0.558 | (-9.895, 6.195) | 1 |

Abbreviations: LDD: Lumbar Disc Degeneration; CI: Confidence Interval

DISCUSSION

The process of LDD is multifactorial and chronic including intrinsic and extrinsic determinants. A number of environmental factors may contribute to etiology and pathological of disc degeneration, such as mechanical overloading, age, obesity, smoking status, but it is still far from being clear at present [19-21]. Recently, many polymorphisms in genes have been shown to be associated with LDD, which will bring positive significance for the prevention and treatment of LDD [22,23]. Previous studies have reported the GDF5 genetic polymorphisms play a critical role in etiology and pathogenesis of disc degeneration [18]. The association between GDF5 gene polymorphism and LDD susceptibility has been validated in large-sample epidemiological studies with diverse ethnic backgrounds. In the present study, a meta-analysis was designed in order to update and investigate the correlation between the GDF5 +104T/C polymorphism and the susceptibility to LDD in different ethnic populations. Six studies related to GDF5 +104T/C polymorphism were included with a total of 1107 LDD patients and 4353 controls in the present meta-analysis. It revealed significant evidence of association between the GDF5 +104T/C polymorphism and LDD. These results indicate that T allele of GDF5 was significantly related to a higher risk for LDD in Caucasian and Asian subjects. In the subgroup analysis by ethnicity, GDF5 +104T/C polymorphism was still found to be significantly related to LDD in Caucasian and Asian subjects, although not significantly related to LDD in Caucasians when evaluated using a dominant model (TT vs. TC+CC: OR = 1.00, 95 % CI = 0.78-1.28, $P = 0.99$). Moreover, effects sizes in Asian populations were detected to be consistently greater than in Caucasian populations, suggesting that this gene polymorphism may play different roles in LDD susceptibility among different ethnic origins.

Heterogeneity is a potential problem to be considered when comprehending the results of meta-analyses. In this meta-analysis, significant heterogeneity between different studies existed in the overall population when using an allele model (T vs. C) and a recessive model (TT vs. TC+CC). After subgroups analysis by ethnicity, the heterogeneity had attenuated or disappeared in populations of Caucasian or Asian descent. That means ethnicities with different genetic background might contribute to the heterogeneity. Moreover, we carried out sensitivity analyses for GDF5 +104T/C. Removal one single study from the overall pooled analysis each time do not impact on overall outcomes, suggesting the reliability and stability of the results.

Some limitations of this meta-analysis should be acknowledged. First, the number of published studies included was small for a comprehensive analysis. Some unpublished, non-English, conference articles or studies without sufficient original data were not included in our meta-analysis, which may lead to a bias of our results. Second, we failed to conduct stratification analysis by age, sex, smoking status, obesity, physical load, or other lifestyle factors because of the data limitation of the included studies. Third, other polymorphic loci and environmental factors have been associated with LDD. We could not address gene-gene or gene-environmental interactions in this meta-analysis due to the lack of relevant information. Therefore, additional studies with larger sample sizes of lumbar disc degeneration and controls are required.

In summary, the current meta-analysis comprehensively suggests that the GDF5 +104T/C polymorphism is significantly associated with risk of LDD susceptibility, particularly in Asians. Because of the limitations of this study, future research on GDF5

+104T/C polymorphisms and LDD susceptibility are necessary and gene-gene and/or gene-environmental interactions of other genetic and environmental factors should be investigated.

MATERIALS AND METHODS

Literature Searching Strategy

Potentially relevant studies were selected by PubMed, EMBASE, Web of science, the Cochrane Library Chinese National Knowledge Infrastructure (CNKI) databases up to 10th April 2017. The following keywords were used: (“GDF5” or “growth differentiation factor 5” or “rs143383” or “+104T/C”) and (“polymorphism” or “SNPs” or “single nucleotide polymorphisms”) and (“disc degeneration” or “disc” or “disc herniation” or “intervertebral disc degeneration” or “low back pain”). In addition, manually screening of the references in selected articles were performed for other potentially relevant papers. All research was limited to English and Chinese.

Inclusion and Exclusion Criteria

The studies meeting the following inclusion criteria were included: (1) the study should evaluate the relationship between GDF5 gene +104T/C polymorphism and susceptibility of the LDD; (2) independent case-control studies for humans; (3) sufficient data on genotype distributions in both cases and controls for calculating an odds ratio (OR) with 95% confidence interval. We excluded reviews, case reports, abstracts or animal studies. If studies were duplicated or overlapped publications, the most recent publications were included. All identified studies were selected by two investigators independently.

Data Extraction

According to the inclusion and exclusion criteria, two investigators (Liang and Deng) reviewed and extracted data independently. The following information was extracted from each study: the first author's name, year of publication, country, ethnicity, source of control; study design, sample size, allele numbers and genotype frequencies in cases and controls. When any inconsistencies appeared, we resolved it through discussion. If not, a third reviewer was invited to make a final decision.

Statistical Analysis

The Hardy-Weinberg equilibrium (HWE) in controls for each study was assessed by a goodness of fit chi-square test before statistical analysis. Pooled ORs with 95% CIs were calculated to estimate the strength of association between GDF5+104T/C polymorphism and susceptibility of LDD under five models: TT vs. CC, TT+TC vs. CC, TT vs. CC+TC, allele T vs. allele C and TC vs. CC. $P < 0.05$ was considered as statistically significant. Z-test was used to evaluate the significance of the pooled OR. I²-statistics and Q-test were used to evaluate the statistical heterogeneity among studies, which was considered as significant when $PQ < 0.10$ or $I^2 > 50\%$ [24]. Then, the overall or pooled OR was obtained by a random-effect (DerSimonian-Laird method) in the presence of heterogeneity ($PQ < 0.10$ or $I^2 > 50\%$).

Otherwise, a fixed-effect model (Mantel-Haenszel method) [liwen3-18] was selected ($PQ > 0.05$ or $I^2 < 50\%$) [25]. To further test that relationship and explore the sources of heterogeneity, we performed subgroup analysis based on ethnicity. Sensitivity analyses were performed to assess the influence of each single study on pooled results. We used Begg's funnel plot and Egger's test to measure potential publication bias [26,27]. All statistical

analyses were performed using software RevMan 5.3 (The Cochrane Collaboration) and STATA 12.0 (StataCorp, College Station, TX).

CONCLUSION

There is a strong significant association (OR = 1.80 to 3.70, all $P < 0.05$) in Asian population and weaker associations (OR = 1.20 to 1.64, all $P < 0.05$) in Caucasian population. This meta-analysis suggests an increased risk of GDF5 +104T/C polymorphism against intervertebral disc degeneration among populations especially in Asians.

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AUTHOR CONTRIBUTIONS

Liang contributed to the idea of the current study. Liang and Deng made a search of articles and screened them independently. Any conflict was solved by consulting the senior author (Shao). Deng and Liang extracted data from the six final studies and make tables. Liang and Chen played an important function in analyzing the results and the data analyses and make pictures. Shao polished the draft and approved the final version.

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