Vitamin D receptor gene polymorphisms and the risk of rickets among Asians: a meta-analysis

Song Mao, Songming Huang

ABSTRACT

Aims To evaluate the association between vitamin D receptor (VDR) gene polymorphisms and the risk of rickets among Asians.

Methods Eligible studies were included in our meta-analysis by searching PubMed, Embase, Cochrane and China National Knowledge Infrastructure databases according to a predefined criteria. A random effects model was used to calculate the combined ORs and its corresponding 95% CI.

Results 16 studies were recruited for the analysis of the association between VDR BsmI (rs1544410), TaqI (rs731236), FokI (rs2228570) and Apal (rs7975232) gene polymorphisms and the risk of rickets among Asians, most of whom were from China. B allele/BB genotype was associated with the susceptibility of rickets (p=0.017 and 0.044, respectively), and bb genotype was associated with lower risk of rickets (p=0.033). F allele/FF genotype was associated with the susceptibility of rickets (p<10^-4), and ff genotype was associated with lower risk of rickets (p<10^-4). A allele/AA genotype was associated with the onset of rickets (p=0.044). No significant association was observed between TaqI polymorphism the risk of rickets. A allele/aa genotype was not associated with the risk of rickets. No evidence of publication bias was observed.

Conclusions B allele/BB genotype at the BsmI site, F allele/FF genotype at the FokI site and AA genotype at the Apal site may be risk factors for the onset of rickets among Asians. B allele/BB genotype at the BsmI site and FF genotype at the FokI site may be protective factors against the risk of rickets among Asians.

What is already known on this topic

- Rickets is largely seen in the late stages of vitamin D deficiency. Vitamin D exerts its effect on target tissues through the vitamin D receptor.
- Vitamin D receptor gene polymorphisms are associated with osteoporosis risk, bone mineral density and 25(OH)D concentration.

What this study adds

- B allele/BB genotype at the BsmI site, F allele/FF genotype at the FokI site and AA genotype at the Apal site may be risk factors for the onset of rickets. B allele/BB genotype at the BsmI site and FF genotype at the FokI site may be protective factors against the risk of rickets.

INTRODUCTION

Rickets is a disease of the growing child caused by the failure of mineralisation of bone matrix predominantly seen in the late stages of vitamin D deficiency. Vitamin D regulates calcium and phosphate homeostasis in the body and has a positive impact on bone mineralisation. The deficiency of vitamin D in children is mainly due to insufficient intake of vitamin D and lack of exposure to sunlight, particularly in dark-skinned races. Although vitamin D-fortified milk and food reduce the incidence of rickets, a number of cases develop rickets even under the recommended dose of vitamin D. The available evidence indicates that genetic factors may contribute to the insensitivity to vitamin D supplementation.

The most active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)2D], exerts its effect on target tissues through the vitamin D receptor (VDR). VDR is a ligand-dependent transcription factor and belongs to the steroid hormone receptor superfamily. The liganded VDR results in dimerisation of the receptor, and it forms homodimers or heterodimers with the retinoid X receptor. VDR gene polymorphisms, occurring in intron 8 (BsmI and Apal sites), exon 9 (TaqI site) and exon 2 (FokI site), have been reported to be associated with osteoporosis risk, bone mineral density (BMD) and 25-dihydroxyvitamin D [25(OH)D] concentration. In terms of the possible association between bone metabolism and the linkage disequilibrium of these variants, and the above-mentioned insensitivity to vitamin D supplementation, it is reasonable to hypothesise that the risk of rickets may be associated with the VDR gene polymorphisms. Asians are likely to have lower serum 25(OH)D levels than Caucasians, and they may need longer exposure to sunlight than Caucasians do to increase serum vitamin D levels. Hence, Asians develop more rickets than Caucasians. To date, a number of studies have been performed with the aim of investigating the relationship between VDR (BsmI, TaqI, FokI and Apal) gene polymorphisms and the risk of rickets among Asians. However, the results were in conflict. An improved understanding of this issue may have important clinical implications, given the possibility that VDR gene polymorphisms may be associated with the onset of rickets among Asians. A previous study by Wu et al reviewed the association between VDR gene polymorphisms and the susceptibility of rickets. However, pooled quantitative analysis has not been performed to date. With the accumulating evidence, we therefore
performed this meta-analysis to investigate the association between VDR gene polymorphisms and the susceptibility of rickets among Asians, with the aim of providing a much more reliable finding on the significance of the association.

MATERIALS AND METHODS

Search strategy

We searched the publications that investigated the association of VDR BsmI (rs1544410), TaqI (rs731236), FokI (rs2228570) and Apal (rs7975322) gene polymorphisms with the risk of rickets through April 2013 using PubMed, Embase, Cochrane and China National Knowledge Infrastructure (CNKI) databases. No restriction was imposed on search language. The used search terms were as follows: (1) rickets, vitamin D deficiency, nutritional deficiency; and (2) VDR, gene polymorphism, BsmI, TaqI, FokI and Apal. We searched the relevant articles by combining the terms rickets, vitamin D deficiency or nutritional deficiency and terms BsmI, TaqI, FokI or Apal. We also scrutinised the reference lists of retrieved reviews and articles. If the same participants were enrolled in more than one paper, we chose the study with the most complete analysis.

Inclusion and exclusion criteria

Inclusion criteria: (1) case–control study; (2) the outcome of interest was rickets; (3) the diagnostic criteria for rickets—clinical signs, the change of serum biochemical indexes, bone X-ray or records of rickets; and (4) at least two comparison groups (rickets group vs control group).

Exclusion criteria: (1) case reports, editorials and reviews; (2) hereditary or disease-associated rickets; (3) relationship between other genes and rickets risk; (4) multiple publications of the same data; and (5) study of the role of VDR to diseases.

Data extraction and synthesis

We extracted study characteristics from each study. Data were recorded as follows: first author’s surname, year of publication, ethnicity, number of cases and controls, VDR (BsmI, TaqI, FokI, Apal) genotype. Frequencies of M (B, T, F, A) allele in cases and controls, and HWE (table 1). We assessed the quality of each study included using the Newcastle-Ottawa Quality Assessment Scale, which included the assessment of participants’ selection, exposure and comparability. A study can be awarded a maximum of one score for each category, within the selection and exposure categories. A maximum of two scores can be given for comparability. Two authors independently performed the data extraction and quality assessment, with any disagreements resolved by discussion.

Statistical analysis

OR was used to measure the association between VDR gene polymorphisms and risk of rickets across studies. Heterogeneity of ORs among studies was tested by using the Q statistic (significance level at p<0.10). The F statistic, a quantitative measure of inconsistency across studies, was also calculated. The combined ORs were calculated using a random effects model. In addition, 95% CIs were also calculated. The OR was calculated using three methods: method 1, allele comparison (M allele vs N allele); method 2, comparing MM homozygous with the other two combinations (MM vs MN+NN); and method 3, comparing NN genotype with the other two combinations (NN vs MN+MM). A χ² test using a web-based programme (http://bioinfo.iconcologia.net/index.php?module=Snpsstats; p<0.05 was considered significant) was used to determine whether genotype distribution of the control population conformed to Hardy–Weinberg equilibrium (HWE), which is that the allele and genotype frequencies in a population will remain constant from generation to generation in the absence of other evolutionary influences. Sensitivity analysis was performed when studies with controls were not in HWE (p<0.05). Potential publication bias (a bias with regards to what is likely to be published, among what is available to be published; this bias may distort the results of meta-analyses) was assessed by Egger’s test at the p<0.05 level of significance. All analyses were performed using STATA V.12.0 (Stata Corp, College Station, Texas, USA). p<0.05 was considered statistically significant, except where otherwise specified.

RESULTS

Literature search

We first retrieved 86 relevant citations from the PubMed, Embase, Cochrane and CNKI databases. Of these, 70 studies were excluded according to the inclusion and exclusion criteria; 16 articles were included in our meta-analysis (figure 1). The retrieved data were recorded as follows: first author’s surname, publication year, the number of cases and controls, frequencies of M (B, T, F, A) allele in cases and controls, and HWE (table 1).

Study characteristics for BsmI polymorphism with the risk of rickets

Five12 13 15 18 25 studies were identified for the analysis of the association between BsmI polymorphism and the risk of rickets. A total of 717 cases and 565 controls were included. The average frequency of B allele was 16.5% in cases and 6.45% in controls. The ratio of cases/controls for average frequency of B allele was 2.54.

Study characteristics for TaqI polymorphism with the risk of rickets

Five12 13 15 18 25 studies were identified for the analysis of the association between TaqI polymorphism and the risk of rickets. A total of 414 cases and 419 controls were included. The average frequency of B allele was 16.5% in cases and 6.45% in controls. The ratio of cases/controls for average frequency of B allele was 2.54.

Figure 1 Flow chart of study selection.
average frequency of the T allele was 89.97% in cases and 85.79% in controls. The ratio of cases/controls for average frequency of T allele was 1.05.

Study characteristics for FokI polymorphism with the risk of rickets

Five studies were identified for the analysis of the association between FokI polymorphism and the risk of rickets. A total of 411 cases and 452 controls were included. The average frequency of the F allele was 66.06% in cases and 50.77% in controls. The ratio of cases/controls for average frequency of F allele was 1.3.

Study characteristics for ApaI polymorphism with the risk of rickets

Five studies were identified for the analysis of the association between ApaI polymorphism and the risk of rickets. A total of 233 cases and 365 controls were included. The average frequency of the A allele was 40.77% in cases and 40.27% in controls. The ratio of cases/controls for average frequency of A allele was 1.01.

Quality scale

The number of awarded scores of enrolled studies ranged from 4 to 6 (low quality, 1–3; median quality, 4–6; high quality, 7–9).

Table 1 Characteristics of studies evaluating the effects of VDR gene polymorphisms on the risk of rickets

<table>
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<th>Case MN</th>
<th>Case NN</th>
<th>Control MM</th>
<th>Control MN</th>
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<th>Total MN</th>
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*M=B, N=b.
†M=T, N=t.
‡M=F, N=f.
§M=A, N=a.

BAP, bone alkaline phosphatase; CS, clinical signs; HWE, Hardy-Weinberg equilibrium; RHR, rickets history records; RS, radiographic signs; SC, serum calcium; SP, serum phosphate; VDR, vitamin D receptor.
Association of the ApaI polymorphism with the risk of rickets

A allele/aa genotype was not associated with the risk of rickets (table 3), and AA genotype was associated with the onset of rickets ($p=0.044$, figure 5, table 3).

Publication bias

No significant publication bias was observed ($B$ vs $b$, $p=0.253$; $BB$ vs $Bb+bb$, $p=0.12$; $bb$ vs $BB+Bb$, $p=0.3$; $TT$ vs $Tt+tT$, $p=0.153$; $tt$ vs $TT+Tt$, $p=0.105$; $FF$ vs $Ff+ff$, $p=0.646$; $ff$ vs $FF+Ff$, $p=0.415$; $A$ vs $a$, $p=0.223$; $AA$ vs $Aa+aa$, $p=0.585$; $aa$ vs $AA+Aa$, $p=0.332$).

DISCUSSION

Increasing attention has been focused on the association between VDR gene polymorphisms and the risk of rickets. Several factors may explain the possible contribution of VDR gene polymorphisms to the onset of rickets. First, vitamin D ensures adequate delivery of calcium and phosphate to the bone-forming sites to normally mineralise bone. VDR mediates the action of vitamin D. Hence, the VDR gene polymorphisms might affect the delivery of calcium and phosphate. Mutations in the gene encoding the VDR that interfere with its normal function cause hereditary vitamin D-resistant rickets, a syndrome of severe rickets appearing soon after birth. Also, certain VDR gene polymorphisms were identified to be associated with a lower BMD and the susceptibility of osteoporosis and rheumatoid arthritis (RA). Karray et al reported that the VDR F allele was associated with RA in Tunisians. Wang et al reported that VDR FokI polymorphism was associated with BMD in postmenopausal Asian women. Uysal et al reported that bbAATT and bbTtAa were more frequent in the osteoporosis group than in the control group. Pouresmaeili et al reported that BsmI polymorphism was significantly associated with BMD in the lumbar spine. Jakubowska-Pietkiewicz et al reported that ApaI polymorphism favoured a higher bone mass and better bone structure. All these evidence suggest that VDR gene polymorphisms may affect the bone development, which results in the onset of rickets. Second, VDR gene polymorphisms may influence the 25OH vitamin D concentrations and the response to vitamin D supplementation. Yokoyama et al reported that a significant interaction existed between 1–25OHD levels and FokI polymorphism. Li et al reported that 25(OH)D concentrations were significantly higher in patients carrying the FokI ff genotypes compared with those carrying the FF genotypes. Emerah et al reported that the ABF haplotype was associated with lower 25(OH)D concentrations. Santos et al reported that the BsmI, ApaI and TaqI variants were associated with lower vitamin D levels. Levin et al reported that the associations of low 25-hydroxyvitamin D with major health outcomes may vary according to common genetic differences in the VDR. These facts suggest that VDR gene polymorphisms also affect the levels of vitamin D, leading to vitamin D deficiency. Finally, it is well accepted that the VDR gene polymorphisms influence parathyroid function, which is essential for the metabolism of calcium and phosphate. VDR polymorphisms was proved to show a significant interaction on

Table 2  Quality scale of included studies

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<th>Selection</th>
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<td>AE ACC NRR</td>
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<td>Li et al</td>
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<td>CAD RE SC DC NRR</td>
<td>AE ACC NRR</td>
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ACC, same method of ascertainment for cases and controls; AE, ascertainment of exposure; CAD, case definition adequate; DC, definition of controls; NRR, non-response rate; RE, representativeness of the cases; SC, selection of controls; *, one score.

Figure 2  Forest plot of B allele associated with risk of rickets. The square and horizontal lines correspond to the study-specific OR and 95% CI, respectively.
serum parathyroid hormone. Thus, it would affect the mineralisation of bone indirectly, leading to the dysregulation of bone development. All these data indicate that the VDR gene polymorphisms may be associated with the risk of rickets.

The results from this meta-analysis agreed with the above-mentioned possible mechanisms. For BsmI polymorphism, we found that B allele/BB genotype was associated with the risk of rickets, and bb genotype may be a protective factor against the risk of rickets in Asians. In the past, a number of studies yielded similar results. Hussien et al reported that BMD was significantly lower in individuals with the BB genotype than in Bb heterozygotes and bb genotypes in RA patients with osteoporosis. Arabi et al reported that the least increments of BMD were observed in subjects with BB genotype when supplemented with vitamin D. Lambrinoudaki et al reported that patients with B allele had lower serum levels of 25(OH)D compared with patients with bb genotype. Li et al reported that BMD at the femoral neck was significantly lower in subjects with BB genotype compared with that in subjects with Bb genotype. A meta-analysis by Jia et al showed that bb genotype was associated with a significantly decreased risk of osteoporosis. These previous reports strongly supported the existence of relationship

### Table 3 Meta-analysis of the association of VDR gene polymorphisms with the risk of rickets

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<tr>
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<th>Q test</th>
<th>Model selected</th>
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<td>1.824 (1.112 to 2.994)</td>
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<td>7</td>
<td>0.35</td>
<td>Random</td>
<td>0.823 (0.689 to 0.984)</td>
<td>0.033</td>
</tr>
<tr>
<td><strong>TaqI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T vs t</td>
<td>5</td>
<td>1</td>
<td>Random</td>
<td>0.979 (0.845 to 1.134)</td>
<td>0.775</td>
</tr>
<tr>
<td>TT vs (Tt+TT)</td>
<td>5</td>
<td>0.855</td>
<td>Random</td>
<td>0.997 (0.806 to 1.324)</td>
<td>0.98</td>
</tr>
<tr>
<td>tt vs (Tt+TT)</td>
<td>5</td>
<td>0.813</td>
<td>Random</td>
<td>1.995 (0.941 to 4.229)</td>
<td>0.072</td>
</tr>
<tr>
<td><strong>FokI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F vs f</td>
<td>5</td>
<td>0.309</td>
<td>Random</td>
<td>1.426 (1.206 to 1.686)</td>
<td>&lt;10(^{-4})</td>
</tr>
<tr>
<td>FF vs (Ff+ff)</td>
<td>5</td>
<td>0.603</td>
<td>Random</td>
<td>1.975 (1.485 to 2.627)</td>
<td>&lt;10(^{-4})</td>
</tr>
<tr>
<td>ff vs (Ff+FF)</td>
<td>5</td>
<td>0.558</td>
<td>Random</td>
<td>0.426 (0.320 to 0.691)</td>
<td>&lt;10(^{-4})</td>
</tr>
<tr>
<td><strong>ApaI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A vs a</td>
<td>5</td>
<td>0.216</td>
<td>Random</td>
<td>1.318 (0.902 to 1.941)</td>
<td>0.29</td>
</tr>
<tr>
<td>AA vs (Aa+aa)</td>
<td>5</td>
<td>0.385</td>
<td>Random</td>
<td>1.578 (1.012 to 2.448)</td>
<td>0.044</td>
</tr>
<tr>
<td>aa vs (Aa+AA)</td>
<td>5</td>
<td>0.508</td>
<td>Random</td>
<td>1.967 (0.713 to 1.340)</td>
<td>0.839</td>
</tr>
</tbody>
</table>

VDR, vitamin D receptor.

**Figure 3** Forest plot of tt genotype associated with the risk of rickets. The square and horizontal lines correspond to the study-specific OR and 95% CI, respectively.

**Figure 4** Forest plot of F allele associated with the risk of rickets. The square and horizontal lines correspond to the study-specific OR and 95% CI, respectively.
between BsmI polymorphism and bone metabolism, which is closely related with the onset of rickets. Additionally, the results from sensitivity analysis were similar to those in non-sensitivity analysis regarding the association between BsmI polymorphism and the risk of rickets, which indicated the results were robust.

Our investigation also indicated that F allele/FF genotype at the FokI site and AA genotype at the Apal site were associated with the risk of rickets; ff genotype at the FokI site may play a protective role against the risk of rickets in Asians. Previous studies displayed similar results. Kurt et al. reported that subjects with FF genotype had lower BMD of femoral neck and total hip compared with those with Ft genotype. Montecillo et al. reported that 25(OH)D concentrations were significantly higher in patients carrying the ff genotype compared with patients carrying the FF genotype. Li et al. reported that BMD at the lumbar spine was significantly lower in subjects with ff genotype compared with that in subjects with aa genotype. One study by Singh et al. displayed that FokI polymorphism was associated with BMD of lumbar spine. Furthermore, the results from sensitivity analysis did not change significantly compared with those in non-sensitivity analysis regarding the relationship between FokI polymorphism and the risk of rickets, which indicated the results were robust.

No significant association was observed between TaqI polymorphism with the risk of rickets in our meta-analysis. Similar results were reported in some studies. Jimenez-Salas et al. reported that TaqI polymorphism was not associated with BMD. Diogenes et al. reported that there were no marked influence of TaqI polymorphism on the longitudinal changes in bone mass, bone-related and calcium-related hormones. However, more studies should be performed in the future due to the limited evidence.

Our study has obvious strengths. All the participants were from Asia, and the PCR-RFLP method was used to test the gene polymorphism in all included studies with relatively high quality in terms of the Newcastle-Ottawa Quality Assessment Scale. Another strength was that we calculated the HWE of the control population and performed the sensitivity analysis by excluding the studies with the control population deviating from HWE. The validity of genetic-associated study depends largely on the selection of control population. The genotype distribution of normal control populations should conform to HWE. Trikalinos et al. reported that adjustment for deviation from HWE changed the summary ORs by less than 10% in 33 of 42 meta-analyses; the change ranged from 10% to 31% in the remaining 9 meta-analyses. The deviation from HWE indicates the possibilities of non-random mating, mutation, selection, genetic drift, gene flow and meiotic drive. In a word, the biased sampling led to the non-conforming to HWE. Meanwhile, several limitations should be considered. First, heterogeneities might affect the results of our meta-analysis, although a random effects model had been conducted. The fact that only Chinese/Mongolian/Turkish studies were recruited in this meta-analysis limited the generalisation of our results to other Asian regions. More studies in other regions, such as Indian subcontinent, should be performed in the future. Second, gender affected the incidence of rickets. However, data related to gender were lacking, whereby we were unable to make a subgroup analysis. Finally, although no evidence of publication bias (non-significant tests showed p>0.05) was observed, the relatively small number of participants decreases the statistical power.

Taken together, this meta-analysis suggests that B allele/BB genotype at the BsmI site, F allele/FF genotype at the FokI site and AA genotype at the Apal site may be associated with the onset of rickets in Asians; bb genotype at the BsmI site and ff genotype at the FokI site may play a protective role against risk of rickets in Asians. However, more studies should be performed in the future to confirm our findings.

Competing interests None.

Patient consent Obtained.

Grievance and peer review Not commissioned; externally peer reviewed.

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Mao S, Huang S. Vitamin D receptor gene polymorphisms and the risk of rickets among Asians: a meta-analysis (Arch Dis Child 2014;99:232–8). Dr Songming Huang has advised that although he agreed to be listed as the correspondence author he should not have been named as a co-author of this publication because he made no contributions to it.

He and Song Mao have asked for the article to be retracted on the ground that data included in it and its conclusions are to a significant degree the same as those previously published in Chin J Evid Based Pediatr 2011;6:4.

Arch Dis Child 2014;99:301. doi:10.1136/archdischild-2013-304379