Association Between the TaqI (rs731236 T>C) Gene Polymorphism and Dental Caries Risk: A Meta-analysis

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Objective: This study investigated the association of the TaqI (rs731236 T>C) polymorphism in the VDR gene with dental caries.

Methods: A comprehensive literature search was performed in PubMed, Web of Science, Embase, SinoMed (the Chinese biomedical literature service system), and the Wiley Online Library. Overall comparisons and subgroup analyses based on ethnicity and the presence of dental caries in dentition were performed. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess associations between gene polymorphisms and the risk of dental caries.

Results: Seven articles were included in this meta-analysis. The pooled results revealed a significant association of the TaqI (rs731236 T>C) polymorphism with dental caries in the allele contrast model (C vs. T: OR = 1.24, 95% CI = 1.07–1.44, \( I^2 = 42\% \), \( p = 0.005 \)) and in the recessive genetic model (CC vs. TT/CT: OR = 1.38, 95% CI = 1.03–1.84, \( I^2 = 0\% \), \( p = 0.03 \)). A stratified analysis based on ethnicity revealed a significant association between the TaqI (rs731236 T>C) polymorphism and the risk of dental caries in Asians (C vs. T: OR = 1.28, 95% CI = 1.06–1.54, \( I^2 = 60\% \), \( p = 0.009 \)). Subgroup analysis based on the presence of dental caries in dentition found a significant association of the TaqI (rs731236 T>C) polymorphism with permanent tooth caries in the allele contrast model (C vs. T: OR = 1.40, 95% CI = 1.11–1.77, \( I^2 = 76\% \), \( p = 0.005 \)) and the recessive genetic model (CC vs. TT/CT: OR = 1.44, 95% CI = 1.03–2.00, \( I^2 = 0\% \), \( p = 0.03 \)).

Conclusion: The results of this meta-analysis suggest that the C allele and CC genotype of the TaqI (rs731236 T>C) polymorphism in the VDR gene are associated with an increased risk of dental caries.

Keywords: dental caries, polymorphism, TaqI (rs731236 T>C), meta-analysis

Introduction

The World Health Organization (WHO) lists dental caries as the third leading major disease that seriously affects human health (after cancer and cardiovascular disease). According to the WHO, the decayed-missing-filled index decreased worldwide with the development of stomatology, but dental caries still affect the physical attributes and quality of life of 60–90% of school-aged children and most adults (Petersen, 2003). Untreated dental caries may lead to a series of problems, such as pain, malocclusion, tooth loss, and abscesses, which affect growth and development in children (Sheiham, 2006; Opal et al., 2015; Zhang et al., 2020). Caries is a complex and multifactorial disease caused by environmental factors, such as cariogenic bacteria, diet, oral hygiene and host factors, and genetic factors. However, some people are more likely to be affected with caries when exposed to similar environmental risk factors (Gustafsson et al., 1954; Yildiz et al., 2016). Increasing evidence indicates that hereditary factors may be linked to caries susceptibility (Piekoszewska-Ziętek et al., 2017), and >40% of caries risk is due to genetic factors (Bretz et al., 2005). Some dental caries susceptibility genes were studied. These genes are related to amelogenesis, mineralization, immune reaction, taste, and saliva (Vieira et al., 2014).

Vitamin D plays an important role in tooth formation, especially in the calcification of enamel and dentin (Berdal et al., 1987), and it controls the expression of classical 1,25(OH)2D3.
target genes and dental proteins in the body (Papagerakis et al., 2002). The teeth of vitamin D-deficient rats show obvious variations and abnormalities in morphogenesis and cell differentiation (Berdal et al., 1987). A meta-analysis found that vitamin D supplementation reduced the risk of dental caries by 47% (Hujoel, 2013). The standard level of vitamin D in the blood is also related to dental caries (Schroth et al., 2016). The biological functions of vitamin D are regulated through interactions with the vitamin D3 receptor (VDR) protein (Sutton and MacDonald, 2003). However, nutritional vitamin D deficiency or VDR gene mutations may lead to impaired function of the vitamin D pathway (Wharton and Bishop, 2003). The VDR gene is located on chromosome 12q13.11, and it contains two promoter regions, eight protein-coding exons, and six untranslated exons (Martelli et al., 2014). More than 200 polymorphic sites are found in the VDR gene, and the TaqI (rs731236 T>C) polymorphism is the most studied variant (Qin et al., 2019). TaqI polymorphism is characterized by a single base transition (T>C) that leads to a synonymous change at codon 352 in exon 9, which was significantly associated with several diseases, such as periodontitis, osteoporosis, and multiple sclerosis (Wang et al., 2009; Zhang et al., 2019; Jiang et al., 2020). The T allele is associated with increased transcriptional activity, mRNA stability, and a high serum level of 1,25(OH)2D3 (Martelli et al., 2014).

A considerable number of studies evaluated the association of the TaqI (rs731236 T>C) polymorphism with dental caries. However, their conclusions are not consistent. Therefore, we performed a meta-analysis to examine the associations between TaqI (rs731236 T>C) polymorphism and dental caries.

Materials and Methods

Search strategy

We performed a literature search in PubMed, Web of Science, Embase, SinoMed (the Chinese biomedical literature service system), and Wiley Online Library; the search was updated on August 31, 2020. The following search terms were used to identify relevant articles: “TaqI,” “rs731236,” “gene polymorphism,” “dental caries,” “caries,” and “decayed tooth.” We also screened the references cited in the retrieved articles to identify additional qualified studies. Gray literature and other unpublished studies were not included. The publication language was restricted to English and Chinese. We included Chinese as a publication language because of its large population. However, eligible Chinese literature was not searched. Any disagreements between the two investigators were resolved through discussions with another reviewer (Y.X.). The study was performed using the following PICO model:

Population (P): children and adults
Intervention (I): TaqI (rs731236 T>C) polymorphism
Comparison (C): TaqI (rs731236 T>C)
Outcome (O): Susceptibility to dental caries

Inclusion and exclusion criteria

There was no population limit. The following inclusion criteria for eligible studies were used: (1) the study focused on the association of the TaqI (rs731236 T>C) polymorphism with the risk of caries; (2) case–control studies; and (3) studies with available data to calculate the odds ratios (ORs), 95% confidence intervals (CIs), and p-values. The following exclusion criteria were used: (1) reports that were not case–control studies; (2) case reports, editorials, reviews, and other nonoriginal studies; and (3) duplicate studies.

Data extraction

Two investigators (W.L. and H.T.) separately collected the available data using a predetermined protocol. The following items were included: the surname of the first author, publication year, country, ethnicity, age, genotyping method, number of cases, number of controls, and p-value for Hardy–Weinberg equilibrium (HWE) in the control group.

Methodological quality

Two reviewers (W.L. and H.T.) independently assessed the quality of the literature on the basis of the Newcastle-Ottawa Scale (NOS) criteria (Table 1). Any differences were resolved by discussion. The quality of the literature was evaluated with a Newcastle-Ottawa Quality Assessment Scale Case Control Studies.

### Table 1. Newcastle-Ottawa Quality Assessment Scale Case Control Studies

| Item                                                                 | Yes | No | Not stated |
|----------------------------------------------------------------------|-----|----|-----------|
| **Selection**                                                        |     |    |           |
| Selection of controls                                                |     |    |           |
| (a) Community controls*                                              |     |    |           |
| (b) Hospital controls                                                |     |    |           |
| (c) No description                                                   |     |    |           |
| **Comparability**                                                     |     |    |           |
| (1) Comparability of cases and controls on the basis of the design or analysis |     |    |           |
| (a) Study controls for the most important factor (HWE in control group)* |     |    |           |
| (b) Study controls for any additional factor (e.g., age, gender, and smoker ratios)* |     |    |           |
| **Exposure**                                                         |     |    |           |
| (2) Same method of ascertainment for cases and controls               |     |    |           |
| (a) Yes                                                              |     |    |           |
| (b) No                                                               |     |    |           |
| **Nonresponse rate**                                                 |     |    |           |
| (a) Same rate for both groups*                                       |     |    |           |
| (b) Nonrespondents described                                         |     |    |           |
| (c) Rate different and no designation                                |     |    |           |

*Indicates one point.
resolved through discussion with another reviewer (Y.X.). The following items were included: (1) population selection, (2) comparability of subjects, and (3) measurement of exposure factors. NOS scores ranged from 0 to 9. A score ≥5 indicated a high-quality study, and studies with a score <5 were classified as low quality.

Statistical analysis

The $p$-value for HWE in the control group in an eligible study was assessed using the chi-squared test. $p < 0.05$ was considered a significant divergence from HWE. The associations of TaqI polymorphism with the risk of dental caries were evaluated using ORs with 95% CIs. We performed a Z-test to calculate the statistical significance of ORs, and $p < 0.05$ was deemed significant. The following models were used for TaqI (rs731236 T>C): allele contrast model (C vs. T), recessive genetic model (CC vs. TT/CT), dominant genetic model (CT/CC vs. TT), homozygous genetic model (CC vs. TT), and heterozygous genetic model (CT vs. TT). We performed subgroup analyses based on ethnicity and the presence of dental caries in dentition. Heterogeneity between the eligible publications was detected using Cochran’s Q statistic and the $I^2$ test. A fixed-effects model was used when the $Q$ test demonstrated $p > 0.05$ or $I^2 < 50\%$. Otherwise, a random-effects model was used. All statistical analyses were performed using RevMan 5.3 software (Cochrane Collaboration) and STATA software 12.0 (STATA Corp., College Station, TX).

Sensitivity analysis and publication bias assessment

A sensitivity analysis was performed to evaluate the stability of the results by successively removing each included study. Begg’s and Egger’s tests were used to detect publication bias.

Results

Study characteristics

A total of 262 relevant publications were collected from the initial database search. The titles and abstracts of 15 articles were evaluated by reviewing, and 6 studies were
Table 3. Newcastle-Ottawa Quality Assessment Scores for the Studies Included in the Meta-analysis

| Study                  | Selection | Comparability | Exposure | Score |
|------------------------|-----------|---------------|----------|-------|
| Aribam (2020)          | ★★★       | ★★★★          | ★★★★     | 6     |
| Qin (2019)             | ★★★       | ★★★★          | ★★★★     | 8     |
| Kong (2017)            | ★★★★      | ★★★★          | ★★★★     | 7     |
| Yu (2017)              | ★★★       | ★★★★          | ★★★★     | 5     |
| Izakovicova Holla (2017)| ★★★      | ★★★★          | ★★★★     | 7     |
| Cogulu (2016)          | ★★★       | ★★★★          | ★★★★     | 6     |

Table 4. Results of Pooled Analysis of Each Polymorphism Based on Five Genetic Models

| Study                  | C vs. T  | OR (95% CI) | p   | CT vs. TT  | OR (95% CI) | p   | CC vs. TT/CT  | OR (95% CI) | p   | OR (95% CI) | p   |
|------------------------|----------|-------------|-----|------------|-------------|-----|---------------|-------------|-----|-------------|-----|
| TaqI/rs731236          |          |              |     |            |              |     |               |              |     |              |     |
| Total                  | 1.24 (1.07–1.44) | 0.005 | 42% | 1.45 (0.96–2.19) | 0.08 | 54% | 1.38 (1.03–1.84) | 0.03 | 80% | 0.83 (0.29–2.40) | 0.74 |
| Ethnicity              |           |              |     |            |              |     |               |              |     |              |     |
| Caucasian              | 1.16 (0.90–1.50) | 0.26 | 0%  | 1.05 (0.65–1.71) | 0.84 | 5%  | 1.33 (0.91–1.95) | 0.14 | 0%  | 0.62 (0.13–3.09) | 0.56 |
| Asian                  | 1.24 (1.07–1.44) | 0.005 | 42% | 1.45 (0.96–2.19) | 0.08 | 54% | 1.38 (1.03–1.84) | 0.03 | 80% | 0.83 (0.29–2.40) | 0.74 |
| Dental caries in dentition | 2.10 (0.87–5.18) | 0.24 | 43% | 1.39 (0.91–2.15) | 0.13 | 43% | 0.80 (0.30–2.12) | 0.54 | 90% | 1.67 (0.96–2.90) | 0.07 |
| Deciduous              | 1.26 (0.97–1.52) | 0.23 | 0%  | 1.37 (0.81–2.33) | 0.24 | 0%  | 1.23 (0.95–2.26) | 0.03 | 0%  | 1.67 (0.99–2.87) | 0.07 |
| Mixed caries           | 1.40 (1.11–1.73) | 0.005 | 76% | 1.78 (1.38–2.33) | 0.04 | 89% | 1.44 (1.03–2.00) | 0.04 | 100% | 1.63 (0.83–3.30) | 0.03 |

Quantitative data synthesis

Seven studies with 1424 cases and 1046 controls were included to assess the association of the TaqI polymorphism with susceptibility to dental caries. The overall comparison found significant statistical evidence of an association between the TaqI polymorphism and dental caries in the allele contrast model (C vs. T: OR = 1.24, 95% CI = 1.07–1.44, I² = 42%, p = 0.005) and the recessive genetic model (CC vs. TT/CT: OR = 1.38, 95% CI = 1.03–1.84, I² = 0%, p = 0.03).

No significant association of TaqI (rs731236 T>C) polymorphism with dental caries was found in the other three genetic models (dominant genetic model, CT/CC vs. TT: OR = 1.45, 95% CI = 0.96–2.19, I² = 54%, p = 0.08; homozygous genetic model, CC vs. TT: OR = 0.83, 95% CI = 0.29–2.40, I² = 0%, p = 0.74; heterozygous genetic model, CT vs. TT: OR = 1.41, 95% CI = 0.89–2.22, I² = 59%, p = 0.14).

A stratified analysis based on ethnicity found a significant association between the TaqI (rs731236 T>C) polymorphism and the risk of dental caries in Asians (C vs. T: OR = 1.28, 95% CI = 1.06–1.54, I² = 60%, p = 0.009; Fig. 2). The pooled results are presented in Table 4 of this subgroup analysis based on the presence of dental caries in dentition revealed a significant association of the TaqI (rs731236 T>C) polymorphism with permanent tooth caries in the allele contrast model (C vs. T: OR = 1.40, 95% CI = 1.11–1.77, I² = 76%, p = 0.005; Fig. 3) and recessive genetic model (CC vs. TT/CT: OR = 1.44, 95% CI = 1.03–2.00, I² = 0%, p = 0.03). No significant association of the TaqI (rs731236) polymorphism with deciduous tooth decay or mixed tooth caries was found in the five genetic models (Table 4).
FIG. 2. Forest plot of association between TaqI polymorphism and dental caries risk based on ethnicity (C vs. T).

FIG. 3. Forest plot of association between TaqI polymorphism and dental caries risk based on dental caries in dentition (C vs. T).
Sensitivity analysis

A sensitivity analysis was performed to evaluate the influence of each study by sequentially removing each included study. The significance of the pooled ORs was not affected by excluding any eligible article. Therefore, the present meta-analysis obtained stable and credible results (Fig. 4).

Publication bias

We performed Begg’s test and Egger’s test to detect the publication bias of each study (Figs. 5, 6). We did not detect notable publication bias for the TaqI (rs731236 T>C) polymorphism in any genetic model. All p-values from Begg’s test and Egger’s test are given in Table 5.

Discussion

Dental caries is a multifactorial disease that includes genetic and environmental factors. Vitamin D deficiency is related to enamel hypoplasia, which is associated with an increased risk of caries (Purvis et al., 1973; Hong et al., 2009). The VDR gene mediates the biological function of the vitamin D metabolite, which is related to normal enamel formation (Uitterlinden et al., 2004; Hujoel, 2013). Polymorphisms of VDR in humans lead to genetic abnormalities and phenotypic diversity in tooth enamel (Zhang et al., 2009). The roles of VDR gene polymorphisms in caries epidemiology attracted considerable attention in recent years. A number of studies on the associations of VDR gene polymorphisms, such as FokI, ApaI, BsmI, Cdx2, and TaqI, with the susceptibility to dental caries were published, and the TaqI (rs731236 T>C) polymorphism was the most studied variant. However, the results of these studies were inconclusive.

To our knowledge, this study is the first comprehensive study to investigate the possible association of the TaqI (rs731236 T>C) polymorphism with dental caries risk. Of the seven studies included in the meta-analysis of TaqI (rs731236 T>C), three studies indicated an association of the TaqI (rs731236 T>C) variant with an increased risk of dental caries (Hu et al., 2015; Cogulu et al., 2016; Aribam et al., 2020). Four studies showed that TaqI gene mutations could not be used as a marker for increased dental caries risk (Izakovicova Holla et al., 2017; Kong et al., 2017; Yu et al., 2017; Qin

FIG. 4. Sensitivity analysis for TaqI polymorphism and dental caries risk in an allelic model (C vs. T).

FIG. 5. Begg’s funnel plot of the TaqI polymorphism and dental caries risk in an allelic model (C vs. T).
et al., 2019). Our meta-analysis results showed a significant association between the TaqI (rs731236 T>C) polymorphism and the risk of dental caries under the allele contrast (C vs. T) and recessive (CC vs. CT/TT) models. The ethnicity subgroup analysis showed that the TaqI (rs731236 T>C) polymorphism was significantly associated with the risk of dental caries in Asians but not in Caucasians. These results may reflect geographical and ethnic differences. The allele contrast (C vs. T) and recessive (CC vs. CT/TT) models found a statistically significant difference for the permanent dentition subgroup. Notably, these effects were not obtained in the deciduous dentition or mixed dentition subgroups. Bayram et al. (2015) and Borilova Linhartova et al. (2016) showed that the influence of genetic factors on enamel caries was different between deciduous and permanent teeth. Insertion/deletion (I/D) polymorphisms of angiotensin-converting enzyme may be related to dental caries in permanent teeth but not in deciduous teeth, especially in females in the Czech population (Borilova Linhartova et al., 2016).

The main purpose of performing this meta-analysis was to improve the statistical power and obtain more compelling results by increasing the sample size. However, some latent shortcomings of this research cannot be ignored when interpreting the results. First, although we performed a systematic and comprehensive literature search, the number of studies that were ultimately included in the meta-analysis was limited. Second, dental caries is a multifactorial disease. However, the influence of gene–gene and gene–environment interactions was not resolved in our meta-analysis due to a lack of available data. Therefore, the potential role of the TaqI (rs731236 T>C) polymorphism may obscure or amplify other gene–gene/gene–environment interactions. Third, although there was no obvious publication bias according to the funnel plot and Egger’s test, potential sources of bias may exist because only published studies were retrieved.

Conclusion

The results of this study suggested that TaqI (rs731236 T>C) polymorphism was associated with an increased risk of dental caries. Because of the study limitations, the conclusions of this meta-analysis should be cautiously interpreted. Future studies with larger sample sizes and more ethnic groups are required to achieve more convincing and realistic statistical analyses. The underlying molecular mechanisms of the association between the TaqI (rs731236 T>C) polymorphism and dental caries risk should also be examined.

Authors’ Contributions

W.L. and H.T. performed the literature search, study selection, data collection, and statistical analysis and wrote the article. Y.X. conceived and designed this study and revised the article.

Author Disclosure Statement

No competing financial interests exist.

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