Matrix metalloproteinase gene polymorphisms and periodontitis susceptibility: a meta-analysis involving 6,162 individuals

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We aimed to systematically investigate the potential association of matrix metalloproteinase (MMP)-9, -3, -2, and -8 gene polymorphisms with susceptibility to periodontitis using meta-analysis. A literature search in PubMed, Embase, and Web of Science was conducted to obtain relevant publications. Finally a total of 16 articles with 24 case-control studies (nine on MMP-9-1562 C/T, seven on MMP-3-1171 A5/A6, four on MMP-2-753C/T, and four on MMP-8-799 C/T) were considered in this meta-analysis. The results based on 2,724 periodontitis patients and 3,438 controls showed that MMP-9-1562 C/T, MMP-3-1171 A5/A6, and MMP-8-799 C/T polymorphisms were associated with periodontitis susceptibility. No significant association was found between MMP-2-753 C/T and periodontitis susceptibility. Subgroup analyses suggested that the MMP-9-1562 C/T polymorphism reduced chronic periodontitis susceptibility and MMP-3-1171 A5/A6 polymorphism increased chronic periodontitis susceptibility. In summary, current evidence demonstrated that MMP-9-753 C/T polymorphism reduced the risk of periodontitis, MMP-3-1171 5A/6A and MMP-8-799 C/T polymorphisms increased the risk of periodontitis, and MMP-2-753 C/T was not associated with risk of periodontitis.

Periodontitis is considered as an inflammatory disease caused by bacterial infection and characterized by loss of connective tissue and alveolar bone1,2. It is classified into two major types, namely chronic periodontitis (CP) and aggressive periodontitis (AgP)3,4, and is generally regarded as one of the most common diseases around the world with a prevalence of 15–20%.6 Of greater importance, periodontitis has been suggested to be associated with other disorders such as head and neck cancer, coronary heart disease, and chronic obstructive pulmonary disease6–9. Therefore, to elucidate the etiology, identify risk factors, and prevent its onset are very important. In the past few years, great efforts had been taken to elucidate potential background leading to the etiology of periodontitis. In addition to bacterial infection, individuals’ susceptibility to periodontitis is likely to be of major importance in determining the manifestation and progression of the disease10. Genetic factors, such as cyclooxygenase-2 gene polymorphisms and interleukin gene polymorphisms had been demonstrated by meta-analyses that whether they were associated with periodontitis susceptibility11–16.

Periodontal health needs a balance between tissue destruction enzymes, e.g. matrix metalloproteinase (MMP), and its inhibitors. The MMP is a family of proteolytic enzymes involved in matrix remodeling and basement membranes in the begging and developing course of a wide range of diseases17. In addition, it has been confirmed to be involved in the pathogenesis of periodontitis18. Many meta-analyses showed that MMP-1 1607 G1/G2 gene polymorphism was associated with CP susceptibility, as well with the severity of disease condition19–20. Regarding MMP-9-1562 C/T polymorphism, a meta-analysis indicated that it had no association with periodontitis18, but another meta-analysis suggested that it might be involved in the development of periodontitis21. Therefore, we determined to perform a meta-analysis with improved quality and to investigate the interaction association between gene polymorphism and environmental factors such as smoking. Moreover, many molecular

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epidemiological studies has been conducted to investigate the association between MMP-3-1171 A5/A6, MMP-8-799 C/T, and MMP-2-753 C/T polymorphisms and periodontitis susceptibility. Nevertheless, the results still remain inconsistency and individual studies based on small sample sizes have low statistical power to investigate the real association. These facts warranted us to perform a meta-analysis to further investigate the role of these polymorphisms in the pathogenesis of periodontitis.

**Methods**
This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in reporting this meta-analysis.

**Eligible criteria.** The following criteria were used for literature selection: 1) articles that explored the association between MMP gene polymorphisms and periodontitis (CP and/or AgP) susceptibility; 2) the study design was cohort or case-control study; 3) there are adequate data to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Two investigators independently screened all papers by title or abstract and then by a full content evaluation. Any discrepancy between the two authors was solved by discussion with a third investigator.

**Search strategy.** A comprehensive electronic database search was conducted for studies that examined associations between MMP polymorphisms and periodontitis. We utilized the PubMed, Embase, and Web of Science citation index to identify papers in which MMP polymorphisms were examined in patients with periodontitis and controls (up to 20 September, 2015). In addition, bibliographies of all potentially relevant studies and recently reviews were reviewed to identify additional articles not indexed by the aforementioned databases. The following text words and MeSH terms were searched: “matrix metalloproteinase” (MeSH term and text word), “MMP” (text word), “genetic, polymorphism” (MeSH term), “polymorphism” (text word), “periodontal disease” (MeSH and text word), and “periodontitis” (MeSH and text word). We limited the search to studies that were carried out on humans and were written in English.

**Data extraction and quality assessment.** Two authors independently extracted the data and assessed the methodological quality. The following data were extracted from each study: first author’s surname, publication year, country, ethnicity, type of disease, source of control, sample size, number of genotype distribution, Hardy-Weinberg equilibrium (HWE) for controls, site of polymorphism, genotyping method, smoking percentile, and other factors for environment. Quality assessment of included studies was evaluated using the Newcastle-Ottawa scale (NOS) by two authors (P = 0.90 for κ test) independently.

**Data Analysis.** A χ² test was used to assess the deviation of genotype distribution from HWE among controls. We performed meta-analyses using allelic contrast, homozygote contrast, heterozygote contrast, recessive, and dominant models. The associations between the polymorphisms and periodontitis risk were assessed by ORs and corresponding 95% CIs. Cochran’s Q metric was used to assess between-tric was used to assess between-study heterogeneity. When the Q metric (P < 0.1) indicated significant heterogeneity among studies, the random-effects
model (the Der-Simonian and Laird method) was applied to perform the meta-analysis. If the between study heterogeneity was not significant \((P \geq 0.1)\), the fixed-effects model (Mantel-Haenszel method) was used. We quantified the degree of heterogeneity using \(I^2\) statistic\(^{24}\). \(I^2\) ranges between 0 and 100%, and stands for the proportion of inter-study variability attributable to heterogeneity rather than random error. \(I^2\) values of 75%, 50%, and 25% were defined as high, moderate, and low estimates, respectively. If the number of included studies was applicable, we conducted stratified analyses on the bias of type of disease, ethnicity, agreement with HWE for controls, source of control, severity of CP, smoking status, and genotyping method. Funnel plots are used to detect publication bias. In addition, we performed Egger's linear regression test to measure the asymmetry of funnel plot \((P < 0.05)\)\(^{25}\). The meta-analysis was conducted using the Stata 12.0 software (Stata Corp LP, College Station, TX, USA), and the \(P\) value was two-sided.

**Results**

**Study identification and characteristics.** As shown in Fig. 1, we initially identified 142 articles. Finally we included 16 articles\(^{26-41}\) with 24 case-control studies involving 2,724 cases and 3,438 controls. Among them, there were four polymorphisms of MMP gene included in our meta-analysis: nine on MMP-9-1562 C/T, seven on MMP-3-1171 A5/A6, four on MMP-2-753C/T, and four on MMP-8-799 C/T. Two of these studies\(^{28,37}\) contained data on two different groups (CP and AgP), which were considered independently. One article contained two independent case-control studies in different countries and in this study only allele number was available\(^{39}\). Three

| Polymorphism | Reference Year Country Ethnicity Disease type Control source Case Control Smoking (%) Genotyping method P value NOS score |
|--------------|-----------------|------------------|------------------|--------------------------|-------------------|-------------------|-------------------|-------------------|
| MMP-9-1562 C/T | de Souza 2005 Brazil Mixed CP HB 42 20 0 24 13 3 0 0 PCR-RFLP 0.62 7 |
| | Holla 2006 Czech Caucasian CP HB 122 43 4 93 37 5 26.0 29.6 PCR 0.59 8 |
| | Keles 2006 Turkish Caucasian CP HB 57 13 0 42 24 4 NA NA PCR 0.82 7 |
| | Chen 2007 China Asian AgP PB 62 15 2 101 26 1 NA NA PCR-RFLP 0.63 7 |
| | Gurkan 2007 Turkish Caucasian AgP HB 58 53 1 78 72 7 32.6 5.1 PCR 0.06 7 |
| | Gurkan 2008 Turkish Caucasian CP PB 54 32 1 52 52 3 47.1 3.7 PCR 0.02 6 |
| | Loo 2011 China Asian CP PB 143 73 64 43 72 135 NA NA PCR-RFLP <0.01 6 |
| | Isaza-Guzman 2011 Colombia Mixed CP HB 58 11 0 47 6 1 14.6 4.9 PCR-RFLP 0.16 7 |
| | Li 2012 China Asian CP PB 68 26 28 99 156 277 93.4 97.7 PCR-RFLP <0.01 6 |
| MMP-3-1171 A5/A6 | Itagaki 2004 Japan Asian AgP HB 0 17 20 4 38 100 NA NA Taqman 0.87 8 |
| | Itagaki 2004 Japan Asian CP HB 5 58 142 4 38 100 NA NA Taqman 0.87 8 |
| | Astolfi 2006 Brazil Mixed CP PB 19 52 19 8 70 25 NA NA Taqman 0.87 8 |
| | Loo 2011 China Asian CP PB 154 115 11 100 135 15 NA NA PCR-RFLP <0.01 6 |
| | Li 2012 China Asian CP PB 75 44 3 213 283 36 90.4 97.7 PCR-RFLP <0.01 6 |
| | Letra* 2012 Brazil Mixed CP HB NA NA NA 121 114 64 NA NA Taqman <0.01 6 |
| | Letra* 2012 US Caucasian CP HB NA NA NA 51 91 62 NA NA Taqman 0.13 7 |
| MMP-8-799 C/T | Chou 2011 China Asian CP PB 122 191 48 53 40 13 25.5 15.1 PCR-RFLP 0.22 8 |
| | Chou 2011 China Asian AgP PB 34 50 12 53 40 13 25 15.1 PCR-RFLP 0.22 7 |
| | Holla 2012 Czech Caucasian CP HB 88 163 90 84 134 60 30 28 PCR-RFLP 0.63 8 |
| | Emingil 2014 Turkish Caucasian AgP PB 11 57 32 76 66 25 29 3.6 TaqMan 0.10 8 |
| MMP-2-753 C/T | Holla 2005 Czech Caucasian CP PB 107 38 4 93 30 4 NA NA PCR-RFLP 0.42 8 |
| | Chen 2007 China Asian AgP PB 63 15 1 98 28 2 NA NA PCR-RFLP 1.00 7 |
| | Gurkan 2007 Turkish Caucasian AgP HB 49 39 4 98 54 5 32.6 5.1 PCR 0.06 7 |
| | Gurkan 2008 Turkish Caucasian CP PB 51 32 4 67 37 3 47.1 3.7 PCR 0.43 6 |

Table 1. Characteristics of the studies included in the meta-analysis. CP = chronic periodontitis, AgP = aggressive periodontitis, NA = not available, HB = hospital-based, PB = population-based. \(P\) for Hardy-Weinberg equilibrium, *Only allele number available in controls.
| Genetic Model and Subgroup | Subgroups | N | Test of Association | Test of Heterogeneity |
|---------------------------|-----------|---|----------------------|-----------------------|
|                           |           |   | **OR** | **95% CI** | **P** | **Model** | **P** | **I^2 (%)** | **P** |
| T vs. C                   | Overall   | 9 | 0.58 | 0.37–0.90 | 0.015 | R | <0.001 | 82.2 | 0.039 |
|                           | HWE (yes) | 6 | 0.8 | 0.64–1.00 | 0.052 | F | 0.198 | 31.6 | |
|                           | AgP       | 2 | 0.93 | 0.67–1.29 | 0.656 | F | 0.496 | 0 | |
|                           | CP        | 7 | 0.49 | 0.31–0.77 | 0.002 | R | <0.001 | 85.8 | |
|                           | Caucasian | 4 | 0.72 | 0.57–0.90 | 0.005 | F | 0.122 | 48.2 | |
|                           | Asian     | 3 | 0.39 | 0.20–0.73 | 0.004 | R | <0.001 | 88.9 | |
|                           | Mixed     | 2 | 0.89 | 0.49–1.59 | 0.684 | F | 0.596 | 0 | |
|                           | HB        | 5 | 0.76 | 0.60–0.97 | 0.027 | F | 0.19 | 34.7 | |
|                           | PB        | 4 | 0.44 | 0.25–0.79 | 0.006 | R | <0.001 | 89.7 | |
|                           | PCR       | 4 | 0.72 | 0.57–0.90 | 0.005 | F | 0.122 | 48.2 | |
|                           | PCR-RFLP  | 5 | 0.52 | 0.29–0.93 | 0.039 | F | 0.122 | 48.2 | |
|                           | Moderate CP | 2 | 0.65 | 0.40–1.07 | 0.09 | F | 0.358 | 0 | |
|                           | Sever CP  | 2 | 0.98 | 0.64–1.50 | 0.926 | F | 0.343 | 0 | |
|                           | Non-smokers | 2 | 0.67 | 0.46–1.00 | 0.048 | F | 0.86 | 0 | |
| TT vs. CC                 | Overall   | 9 | 0.17 | 0.13–0.23 | <0.001 | F | 0.217 | 25.6 | 0.121 |
|                           | HWE (yes) | 6 | 0.4 | 0.18–0.89 | 0.026 | F | 0.405 | 1.7 | |
|                           | AgP       | 2 | 0.74 | 0.05–12.16 | 0.836 | R | 0.082 | 66.8 | |
|                           | CP        | 7 | 0.16 | 0.12–0.22 | <0.001 | R | 0.082 | 66.8 | |
|                           | Caucasian | 4 | 0.3 | 0.12–0.76 | 0.11 | F | 0.578 | 0 | |
|                           | Asian     | 3 | 0.18 | 0.09–0.38 | <0.001 | R | 0.043 | 68.1 | |
|                           | Mixed     | 2 | 0.23 | 0.02–2.25 | 0.206 | F | 0.883 | 0 | |
|                           | HB        | 5 | 0.29 | 0.12–0.72 | 0.008 | F | 0.718 | 0 | |
|                           | PB        | 4 | 0.19 | 0.10–0.36 | <0.001 | F | 0.883 | 0 | |
|                           | PCR       | 4 | 0.12 | 0.02–5.09 | 0.11 | F | 0.578 | 0 | |
|                           | PCR-RFLP  | 5 | 0.16 | 0.00–9.06 | 0.34 | F | 0.831 | 0 | |
|                           | Moderate CP | 2 | 0.16 | 0.00–9.06 | 0.34 | F | 0.831 | 0 | |
|                           | Sever CP  | 2 | 0.75 | 0.20–2.81 | 0.667 | F | 0.563 | 0 | |
|                           | Non-smokers | 2 | 1.38 | 0.38–4.92 | 0.623 | F | 0.579 | 0 | |
| CT vs. CC                 | Overall   | 9 | 0.61 | 0.41–0.93 | 0.02 | R | <0.001 | 74.8 | 0.322 |
|                           | HWE (yes) | 6 | 0.87 | 0.66–1.14 | 0.293 | F | 0.406 | 1.6 | |
|                           | AgP       | 2 | 0.97 | 0.65–1.46 | 0.896 | F | 0.906 | 0 | |
|                           | CP        | 7 | 0.53 | 0.33–0.85 | 0.008 | R | 0.001 | 73.4 | |
|                           | Caucasian | 4 | 0.75 | 0.57–0.99 | 0.009 | R | 0.082 | 36.8 | |
|                           | Asian     | 3 | 0.39 | 0.19–0.80 | 0.01 | R | 0.008 | 79.4 | |
|                           | Mixed     | 2 | 1.09 | 0.56–2.11 | 0.808 | F | 0.453 | 0 | |
|                           | HB        | 5 | 0.85 | 0.64–1.14 | 0.286 | F | 0.285 | 20.4 | |
|                           | PB        | 4 | 0.43 | 0.25–0.76 | 0.004 | R | 0.007 | 75.3 | |
|                           | PCR       | 4 | 0.75 | 0.57–0.99 | 0.004 | R | 0.192 | 36.8 | |
|                           | PCR-RFLP  | 5 | 0.56 | 0.29–1.09 | 0.09 | R | 0.001 | 79.2 | |
|                           | Moderate CP | 2 | 0.7 | 0.39–1.24 | 0.218 | F | 0.319 | 0 | |
|                           | Sever CP  | 2 | 1.06 | 0.64–1.74 | 0.667 | F | 0.414 | 0 | |
|                           | Non-smokers | 2 | 0.87 | 0.66–1.14 | 0.293 | F | 0.406 | 1.6 | |
| TT + CT vs. CC            | Overall   | 9 | 0.54 | 0.32–0.93 | 0.025 | R | <0.001 | 86.9 | 0.104 |
|                           | HWE (yes) | 6 | 0.82 | 0.63–1.06 | 0.133 | F | 0.276 | 20.9 | |
|                           | AgP       | 2 | 0.95 | 0.64–1.42 | 0.814 | F | 0.798 | 0 | |
|                           | CP        | 7 | 0.46 | 0.26–0.82 | 0.009 | R | <0.001 | 85.8 | |
|                           | Caucasian | 4 | 0.71 | 0.54–0.93 | 0.013 | F | 0.134 | 46.2 | |
|                           | Asian     | 3 | 0.32 | 0.13–0.77 | 0.011 | R | <0.001 | 89.9 | |
|                           | Mixed     | 2 | 0.98 | 0.51–1.88 | 0.953 | F | 0.512 | 0 | |
|                           | HB        | 5 | 0.79 | 0.59–1.04 | 0.098 | F | 0.21 | 31.7 | |
|                           | PB        | 4 | 0.37 | 0.17–0.78 | 0.009 | R | <0.001 | 88.8 | |
|                           | PCR       | 4 | 0.71 | 0.54–0.93 | 0.013 | F | 0.134 | 46.2 | |
|                           | PCR-RFLP  | 5 | 0.48 | 0.22–1.07 | 0.072 | R | <0.001 | 88.6 | |
|                           | Moderate CP | 2 | 0.65 | 0.37–1.14 | 0.132 | F | 0.323 | 0 | |
|                           | Sever CP  | 2 | 1.02 | 0.63–1.66 | 0.939 | F | 0.363 | 0 | |

Continued
were more susceptible to CP than AgP (Table 2).

**Table 2. Meta-analysis of the association between the MMP-9-1562 C/T polymorphism and periodontitis.**

| Subgroups | N | OR | 95% CI | P value | Test of Association | Test of Heterogeneity | P* value |
|-----------|---|----|--------|---------|---------------------|-----------------------|----------|
| Non-smokers | 2 | 1.02 | 0.66–1.58 | 0.935 | F | 0.439 | 0 |
| TT vs. CC | Overall | 9 | 0.26 | 0.21–0.36 | <0.001 | F | 0.601 | 0 | 0.379 |
| HWE (yes) | | 6 | 0.41 | 0.18–0.93 | 0.033 | F | 0.437 | 0 |
| AgP | 2 | 0.75 | 0.05–12.36 | 0.372 | R | 0.08 | 67.3 |
| CP | 7 | 0.27 | 0.20–0.35 | <0.001 | F | 0.897 | 0 |
| Caucasian | 4 | 0.33 | 0.13–0.83 | 0.018 | F | 0.624 | 0 |
| Asian | 3 | 0.27 | 0.21–0.36 | <0.001 | F | 0.119 | 53 |
| Mixed | 2 | 0.23 | 0.02–2.22 | 0.202 | F | 0.915 | 0 |
| HB | 5 | 0.3 | 0.12–0.75 | 0.01 | F | 0.753 | 0 |
| PB | 4 | 0.28 | 0.21–0.37 | <0.001 | F | 0.224 | 31.3 |
| PCR | 4 | 0.33 | 0.13–0.83 | 0.018 | F | 0.624 | 0 |
| PCR-RFLP | 5 | 0.27 | 0.21–0.36 | <0.001 | F | 0.368 | 6.7 |
| Moderate CP | 2 | 0.37 | 0.06–2.26 | 0.284 | F | 0.891 | 0 |
| Sever CP | 2 | 0.73 | 0.20–2.72 | 0.64 | F | 0.618 | 0 |
| Non-smokers | 2 | 1.35 | 0.38–4.80 | 0.641 | F | 0.618 | 0 |

articles were focused on two polymorphisms, and two articles were focused on three polymorphisms, which were treated as independent case-control studies as well. Four articles with six case-control studies did not satisfy the HWE for control group. Main characteristics of included studies were summarized in Table 1.

**MMP-9-1562 C/T polymorphism and periodontitis susceptibility.** In all study subjects, meta-analysis showed a reduced risk between the MMP-9-1562 C/T polymorphism and periodontitis susceptibility in all tested genetic model (T vs. C: OR = 0.58, 95% CI = 0.37–0.90; TT vs. CC: OR = 0.17, 95% CI = 0.13–0.23; CT vs. CC: OR = 0.61, 95% CI = 0.41–0.93; TT vs. CT vs. CC: OR = 0.54, 95% CI = 0.32–0.93; TT vs. CC + CT: OR = 0.28, 95% CI = 0.21–0.36) with some evidence of between-study heterogeneity (Table 2). Sensitivity analysis excluding studies with control inconsistent with HWE showed that the decreased risk was only observed in recessive model (OR = 0.41, 95% CI = 0.18–0.93). Stratification analysis by type of disease indicated that individuals were more susceptible to CP than AgP (Table 2).

**MMP-3-1171 A5/A6 polymorphism and periodontitis susceptibility.** Meta-analysis of the MMP-3-1171 A5/A6 polymorphism showed an elevated risk between the polymorphism and periodontitis susceptibility in three tested genetic model (A5 vs. A6: OR = 1.45, 95% CI = 1.26–1.66; A5/A5 vs. A6/A6: OR = 2.32, 95% CI = 1.42–3.81; A5/A5 vs. A6/A5 + A6/A6: OR = 2.03, 95% CI = 1.59–2.59) with low between-study heterogeneity (Table 3). Stratification by disease type indicated that individuals were more susceptible to CP rather than AgP (Table 3).

**MMP-2-753 C/T and MMP-8-799 C/T polymorphisms and periodontitis susceptibility.** Meta-analysis of the MMP-2-753 C/T showed no association between the polymorphism and periodontitis susceptibility (T vs. C: OR = 1.13, 95% CI = 0.88–1.44; TT vs. CC: OR = 1.25, 95% CI = 0.98–1.55; CT vs. CC: OR = 1.14, 95% CI = 1.14, 95% CI = 0.85–1.53; TT vs. TT vs. CC: OR = 1.15, 95% CI = 0.87–1.53; TT vs. CC + CT: OR = 1.18, 95% CI = 0.55–2.56) with no between-study heterogeneity (I² = 0% for all genetic models) (Table 4). The results of stratification analyses according to disease type, ethnicity, and smoking status were similar to the overall results (Table 4).

**Publication bias.** Due to limitations of the quantity of included studies, we just test the publication bias for MMP-9-1562 C/T and MMP-3-1171 A5/A6 polymorphisms. The funnel plots based on allele model for MMP-9-1562 C/T and MMP-3-1171 A5/A6 polymorphism were asymmetry and indicated that publication bias probably existed in the present study. The Egger's test showed there was some publication bias existed in the MMP-9-1562 C/T allele model (Table 2).
Discussion

In the present meta-analysis, we aggregated data from published studies to estimate genetic associations between MMP gene, namely MMP-2-753 C/T, MMP-3-1171 A5/A6, MMP-8-799 C/T, and MMP-9-1562 C/T polymorphisms, and periodontitis susceptibility. Our results provided some evidence to support an elevated risk between periodontitis susceptibility and MMP-3-1171 A5 allele and MMP-8-799 T allele, and a reduced risk between periodontitis susceptibility and MMP-9-1562 T allele. But our study provided no evidence to support an association between MMP-2-753 C/T polymorphism and periodontitis. Appreciable differences were identified in the etiology characteristic between CP and AgP, indicating that there might be different genetic mechanisms between them. In stratified analysis by disease type, their association with susceptibility of CP rather than AgP was observed. For MMP-9-1562 C/T polymorphism, we did not observe any meaningful associations in stratified analysis by ethnicity, severity of CP, and smoking status. The results were similar to MMP-3-1171 A5/A6 and MMP-2-753 C/T polymorphisms for periodontitis susceptibility. However, in stratified analysis by ethnicity and smoking status for MMP-8-799 C/T polymorphism indicated an elevated risk in Asian populations rather than Caucasian populations, and non-smokers rather than smokers.
To our knowledge, this is the first quantitative analysis that assessed the association between MMP-2-753 C/T, MMP-3-1171 A5/A6, and MMP-8-799 C/T polymorphisms and periodontitis susceptibility. With regard to MMP-9-1562 C/T polymorphism, two meta-analyses were published in 2013. Pan et al.\textsuperscript{21} indicated that MMP-9-1562 C/T polymorphism might be involved in the development of periodontitis. However, Song et al.\textsuperscript{19} suggested no association between MMP-9-1562 C/T polymorphism and periodontitis susceptibility. Compared with the previous meta-analyses, we had a larger sample size than them, which increased the statistical power, and we found

![Figure 2. Forest plot for MMP-9-1562 C/T polymorphism associated with periodontitis susceptibility in C versus T allele comparison based on random-effects model.](image)

| Genetic Model and Subgroup | N | T vs. C | OR (95% CI) | F (%) | T vs. CC | OR (95% CI) | F (%) | CT vs. CC | OR (95% CI) | F (%) | CT vs. (CT + TT) | OR (95% CI) | F (%) | TT vs. (CC + CT) | OR (95% CI) | F (%) |
|---------------------------|---|---------|-------------|------|---------|-------------|------|-----------|-------------|------|-----------------|-------------|------|-----------------|-------------|------|
| **MMP-2-753 C/T**        |   |         |             |      |         |             |      |           |             |      |                 |             |      |                 |             |      |
| Total                     | 4 | 1.13 (0.88–1.44) | 0 | 1.25 (0.58–2.73) | 0 | 1.14 (0.85–1.53) | 0 | 1.15 (0.87–1.53) | 0 | 1.18 (0.55–2.56) | 0 |
| CP                        | 2 | 1.11 (0.79–1.55) | 0 | 1.20 (0.43–3.37) | 0 | 1.12 (0.74–1.68) | 0 | 1.12 (0.76–1.66) | 0 | 1.16 (0.42–3.24) | 0 |
| AgP                       | 2 | 1.15 (0.81–1.64) | 29.9 | 1.33 (0.41–4.31) | 32.8 | 1.18 (0.77–1.79) | 39.3 | 1.21 (0.38–3.88) | 0 |
| Caucasian                 | 3 | 1.19 (0.91–1.55) | 0 | 1.33 (0.58–3.03) | 0 | 1.23 (0.89–1.69) | 0 | 1.23 (0.90–1.69) | 0 | 1.24 (0.55–2.80) | 0 |
| Asian                     | 1 | 0.84 (0.45–1.58) | NA | 0.78 (0.07–8.76) | NA | 0.83 (0.41–1.68) | NA | 0.83 (0.42–1.66) | NA | 0.81 (0.07–9.06) | NA |
| Non-smokers               | 3 | 1.27 (0.92–1.75) | 0 | 1.38 (0.52–3.62) | 0 | 1.35 (0.91–2.00) | 0 | 1.35 (0.92–1.97) | 0 | 1.24 (0.48–3.22) | 0 |
| Smokers                   | 1 | 0.85 (0.36–1.99) | NA | 1.10 (0.09–13.00) | NA | 0.73 (0.26–2.08) | NA | 0.77 (0.28–2.10) | NA | 1.21 (0.10–14.00) | NA |
| **MMP-8-799 C/T**         |   |         |             |      |         |             |      |           |             |      |                 |             |      |                 |             |      |
| Total                     | 4 | 1.61 (1.11–2.35) | 81.6 | 2.26 (1.03–4.97) | 80.8 | 2.18 (1.19–4.00) | 81.5 | 2.22 (1.21–4.08) | 94.5 | 1.44 (0.90–2.16) | 47.3 |
| CP                        | 2 | 1.28 (1.07–1.54) | 0 | 1.48 (1.02–2.15) | 0 | 1.52 (0.86–2.69) | 72 | 1.48 (1.13–1.95) | 59.9 | 1.25 (0.90–1.73) | 0 |
| AgP                       | 2 | 2.01 (0.98–4.11) | 85.3 | 3.60 (0.61–21.33) | 88.4 | 3.34 (1.11–10.04) | 81.7 | 3.45 (0.95–12.55) | 87.9 | 1.73 (0.68–4.42) | 70.2 |
| Caucasian                 | 2 | 1.84 (0.78–4.32) | 93.8 | 3.44 (0.58–20.47) | 93.2 | 2.55 (0.51–12.76) | 93.6 | 2.82 (0.53–14.96) | 94.5 | 1.79 (0.89–3.61) | 75 |
| Asian                     | 2 | 1.43 (1.11–1.85) | 0 | 1.54 (0.89–2.67) | 0 | 2.03 (1.40–2.93) | 0 | 1.91 (1.35–2.70) | 0 | 1.07 (0.64–1.79) | 0 |
| Non-smokers               | 4 | 1.79 (1.19–2.69) | 79.4 | 2.88 (1.21–6.84) | 78.3 | 2.37 (1.24–4.55) | 77.2 | 2.52 (1.30–4.88) | 80.5 | 1.64 (1.19–2.25) | 38.7 |
| Smokers                   | 1 | 0.91 (0.58–1.42) | NA | 0.81 (0.33–2.00) | NA | 0.96 (0.46–1.99) | NA | 0.91 (0.46–1.82) | NA | 0.84 (0.39–1.81) | NA |

Table 4. Meta-analysis of the association between the MMP-2-753C/T and MMP-8-799C/T polymorphisms and periodontitis. OR = odds ratio, CI = confidence interval, CP = chronic periodontitis, AgP = aggressive periodontitis, NA = not available.
a reduced risk of MMP-9-1562 T allele with periodontitis susceptibility. Genetic association researches designed to investigate relations between gene polymorphisms and complex outcomes must be interpreted with caution, because many factors could potentially affect the results. Therefore, we assessed the association with severity of CP and smoking status even though we did not observe any significant difference among the moderate and severe CP and no association among non-smokers. This might be caused by small sample size that only two studies\textsuperscript{29,33} presented the association between polymorphism and disease severity, two studies\textsuperscript{11,32} investigate the interaction between polymorphism and smoking status.

However, the present meta-analysis also has certain limitations that affect the interpretation of the results. First, the heterogeneity for MMP-9-1562 C/T polymorphism was high. Subgroup analyses suggested that the heterogeneity might come from the deviation of HWE, ethnicity, and genotyping method. Certainly, other clinical heterogeneity also might contribute to it, for instance different classification and diagnosis of periodontitis and differences on the oral examination by different clinicians. In addition, it is widely acknowledged that meta-analysis is a secondary analysis and we could not handle the problem of clinical heterogeneity in a meta-analysis. Therefore, we recommend that further studies should be designed as multi-center studies and utilize unified criterion of disease. Second, although a comprehensive literature search was performed, it was likely that some publications were overlooked because of our language restriction for the literature search. In addition, the number of included studies for each polymorphism was limited. Therefore, the statistic power of present meta-analysis might be affected and the present results might be led to false positive or false negative rate. Third, we used genotype distributions and crude estimates of effect rather than adjusted estimates of association between polymorphism and periodontitis. Even though we investigated the interaction between polymorphism and disease severity and smoking status, the statistic power was limited due to most studies did not present the relevant data. Moreover, age, sex, and gene-gene interactions could not be assessed in our study due to insufficient data. Finally, the publication bias was of concern that small studies with negative results tend not to be published.

In conclusion, this meta-analysis with published data suggested that the MMP-2-753 C/T, MMP-3-1171 A5/A6, and MMP-9-1562 C/T polymorphisms were associated with periodontitis susceptibility and there is lack of association between the MMP-8-799 C/T polymorphism and periodontitis. Further studies with large sample size, gene-gene, and gene-environment detailed information are needed to validate the present results.

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Author Contributions
H.W. and X.-T.Z. designed this study; Y.Y. and Y.-H.J. searched databases and collected full-text papers; X.-Y.M. and D.W.H. extracted and analyzed data; Y.-Y.M. and H.W. wrote the manuscript, X.-T.Z. reviewed the manuscript.

Additional Information
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