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Short Communication

Systematic evaluation of genetic polymorphisms in carcinogen metabolizing enzymes associated with the risk of oral potentially malignant disorders occurrence

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Abstract *Background/purpose:* Accumulated studies investigate the association of single-nucleotide polymorphisms (SNPs) in carcinogen metabolizing enzymes with oral potentially malignant disorders (OPMD) risk. However, these results were inconsistent and conflicting. The purpose of this pooled analysis was to systematically evaluate the associations of SNPs in 6 enzymes (CYP1A1, CYP2E1, GSTM1, GSTM3, GSTT1 and GSTP1) with risk of OPMD occurrence.
Materials and methods: A systematic evaluation was performed to identify all eligible case ndash;control studies on the association between SNPs in 6 enzymes and OPMD onset. Odds ratios (ORs) and 95 % confidence intervals (CIs) were pooled to estimate association strength.

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Results: A significant association of CYP2E1 PstI polymorphism with OPMD was found (OR, 1.46; 95%CI, 1.07–2.00) in 430 cases and 818 health controls. A significant association of GSTM1 null genotype with OPMD, especially oral leukoplakia, was found (OR, 1.72; 95%CI, 1.24–2.37) in 2228 cases and 4425 controls. A significant association of GSTT1 null genotype with OPMD, particularly oral submucous fibrosis, was found (OR, 1.50; 95%CI, 1.01–2.22) in 1798 cases and 3934 controls. A marginally significant association of GSTM3 polymorphism with OPMD was found (OR, 1.41; 95%CI, 1.00–1.98) in 321 cases and 622 controls. There was no significant association of polymorphisms in CYP1A1, CYP2E1 RsaI variant, and GSTP1 with OPMD.
Conclusion: This analysis for the first time investigated SNPs in carcinogen metabolizing enzymes with OPMD, suggesting that polymorphisms in CYP2E1 PstI, GSTM1, GSTM3 and GSTT1 play roles in OPMD occurrence and highlighting their potential in risk stratification and early detection strategies.

Introduction

Oral potentially malignant disorders (OPMD) contain a spectrum of lesions including oral leukoplakia (OLK), oral erythroplakia, and oral submucous fibrosis (OSF), which exhibit a significantly increased risk for malignant transformation to oral squamous cell carcinoma.[1] Environmental risk factors such as tobacco and alcohol use and betel quid chewing deliver carcinogens to the oral mucosa via metabolic activation, inducing genetic mutations, inflammatory responses, and cellular damage that can lead to malignant transformation.[2] The metabolism of these procarcinogens involves bioactivation and detoxification mediated by carcinogen metabolizing enzymes that can detoxify chemical carcinogens within the oral mucosa, which are divided into Phase I and Phase II enzymes.[2] Cytochrome P450 1A1 (CYP1A1) and cytochrome P450 2E1 (CYP2E1) are both vital Phase I enzymes, that convert lipophilic carcinogens into more hydrophilic compounds to facilitate excretion.[3] Glutathione S-transferases (GSTs), mainly four isoenzymes GSTM1, GSTM3, GSTT1 and GSTP1, constitutes the major Phase II metabolism of carcinogens.[4]

Single-nucleotide polymorphisms (SNPs) in carcinogen metabolizing enzymes cause variation in the ability to metabolize carcinogens that render individuals susceptible to OPMD risk.[5] The polymorphisms of *CYP* genes single-nucleotide sites can cause changes in the enzyme activity of CYP1A1 and CYP2E1. The null genotype or variation of *GST* genes could result in the inactivation of GSTM1, GSTM3, GSTT1 and GSTP1 enzymes.[5] Currently, the results of associations between SNPs in these enzymes and OPMD risk remained incomplete and inconsistent. The association of SNPs in *GST* genes with the risk of OLK and OSF was evaluated by a previous meta-analysis, respectively.[6,7] However, there is lack of comprehensive evaluation of SNPs in these enzymes with OPMD risk based on all the available studies. Therefore, to gain more precise evidence for the association, the purpose of this pooled analysis was to systematically evaluate the associations of SNPs in these 6 enzymes with OPMD risk of occurrence based on all eligible case–control studies.

Materials and methods

Search strategy and data extraction

A comprehensive literature search was conducted on PubMed, Medline, and Web of Science databases for all relevant publications on the associations between SNPs and OPMD susceptibility, without any restriction on July 20, 2025. According to the search strategy described in supplementary Table S1, we used medical subject terms (SNP OR polymorphism OR genotyp*) AND (cytochrome P450 OR glutathione OR CYP1* OR CYP2* OR GSTM* OR GSTT* OR GSTP*) AND the synonyms and subtypes of OPMD in all fields. The asterisk indicates a wildcard used to search for all endings including fifth or more root words. In addition, the reference lists given in relevant articles and reviews were also considered for eligible studies. The inclusion criteria for eligible articles were as follows: (i) human case–control studies; (ii) studies on associations of polymorphisms in carcinogen metabolizing genes with OPMD; (iii) sufficient genotyping data for the computation of odds ratio (OR) and 95 % confidence interval (CI); and (iv) histologically confirmed diagnosis of OPMD. On the contrary, the exclusion criteria were as follows: (i) not a human case–control study; (ii) overlapping or duplicate publications; (iii) no genotype data reported; and (iv) the number of the studies on a single gene was <3.

Base on the flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (supplementary Figure S1), 28 eligible case–control studies were retrieved for detailed evaluation from the literature databases (Table S2).[8–35] The following information were extracted from each study: first author' name, publication year, country of origin, ethnicity, genotyping methods, number of cases and controls, age, sex, tobacco and alcohol use, betel quid chewing, source of controls, genotype distributions of cases and controls (supplementary Table S2). Ethical approval and informed consent were not applicable for a meta-analysis.

Statistical analysis

As per the statistical method described previously,[36] the strength of association of SNPs with OPMD susceptibility was determined by OR with 95 % CI. The statistical significance of the pooled OR was evaluated using the Z-test, and the heterogeneity of the ORs was tested by χ^2—based Q-test and I^2 statistics. ORs were pooled according to the fixed-effects model (Mantel-Haenszel model) and random-effects model (DerSimonian-Laird model). Additionally, the potential publication bias was visually examined by the Begg's funnel plot and Egger's test. All statistical analyses were performed with the software Review manager 5.4 (The Cochrane Collaboration, Oxford, UK) using two-sided *P* value, and the value of <0.05 was considered as statistically significant.

Results

Association of polymorphisms in *CYP* genes with OPMD

There were 13 eligible studies on CYP1A1 polymorphism in OPMD onset (Table S2), comprising 949 OPMD patients and 2594 healthy individuals for CYP1A1 MspI variant, and 582 patients with 1148 healthy individuals for the NcoI variant. Overall, no significant association between CYP1A1 MspI polymorphism and OPMD susceptibility was found with the random-effects model (pooled OR, 0.99; 95%CI, 0.59—1.63; $P_{heterogeneity}<0.00001$; Fig. 1A). In the stratified analysis by OPMD categories, similar results were observed in the OLK subgroup (OR, 0.87; 95%CI, 0.33—2.32), the OSF subgroup (OR, 1.50; 95%CI, 0.22—10.05), and the non-specified OPMD subgroup (OR, 0.86; 95%CI, 0.56—1.34). Consistently, no significant association of CYP1A1 NcoI polymorphism with OPMD risk was found with the random-effects model (pooled OR, 1.42; 95%CI, 0.51—3.95; $P_{heterogeneity}<0.00001$; Fig. 1A), with similar findings across all OPMD subgroups.

There were 4 eligible studies on CYP2E1 polymorphism in OPMD onset, including 430 OPMD patients and 818 healthy individuals for CYP2E1 PstI variant, and 355 patients with 668 healthy individuals for the RsaI variant. Overall, a significantly increased risk of CYP2E1 PstI polymorphism with OPMD susceptibility was found with the fixed-effects model (pooled OR, 1.46; 95%CI, 1.07—2.00; $P_{heterogeneity} = 0.19$; Fig. 1B). Stratified analysis revealed a significantly increased risk in the OSF subgroup (OR, 3.14; 95%CI, 1.15—8.62), but not found in the OLK subgroup (OR, 1.35; 95%CI, 0.97—1.88). No significant association of CYP2E1 RsaI polymorphism with OPMD onset was found with the fixed-effects model (pooled OR, 1.24; 95%CI, 0.89—1.72; $P_{heterogeneity} = 0.06$; Fig. 1B). Publication bias was evident for CYP1A1 ($P < 0.05$, Egger's test; Figure S2A), but not CYP2E1 polymorphisms ($P > 0.05$, Egger's test; Figure S2B).

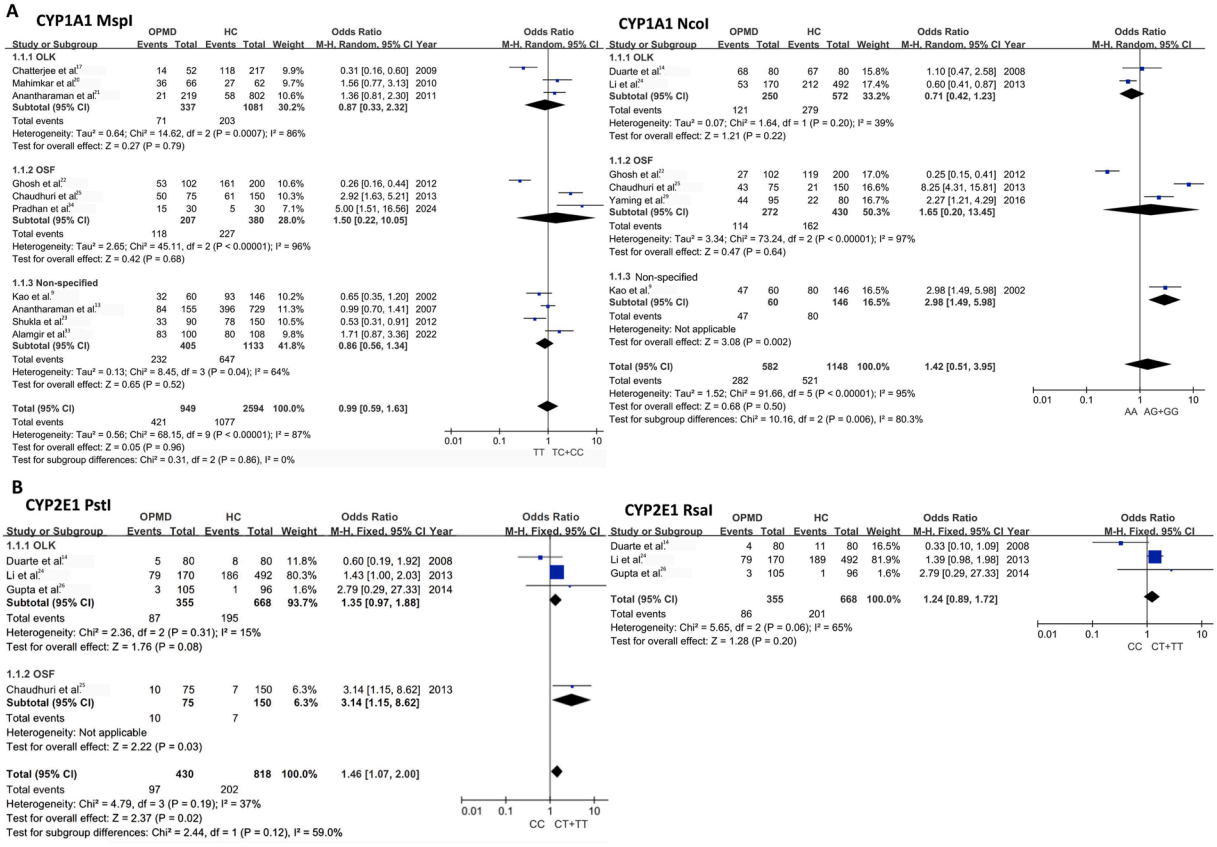

Figure 1 Forest plots of meta-analysis of genetic polymorphisms in Part I carcinogen metabolizing enzymes and oral potentially malignant disorders (OPMD) compared to healthy control. **(A)** CYP2A1 MspI and NcoI, **(B)** CYP2E1 PstI and RsaI. CI, confidence interval. OLK, oral leukoplakia. OSF, oral submucous fibrosis.

Association of polymorphisms in *GST* genes with OPMD

There were 24 eligible studies on GSTM1 polymorphism in OPMD susceptibility (Table S2), containing 2228 OPMD patients and 4425 healthy individuals. Overall, a significant increased risk of OPMD susceptibility with GSTM1 null genotype was found with the random-effects model (pooled OR, 1.72; 95%CI, 1.24–2.37; $P_{heterogeneity}<0.00001$; Fig. 2A). Stratified analysis revealed a significantly increased risk in the OLK subgroup (OR, 1.98; 95%CI, 1.21–3.23), but not in the OSF subgroup (OR, 1.44; 95%CI, 0.90–2.30) and the non-specified OPMD subgroup (OR, 1.24; 95%CI, 0.82–1.88).

There were 18 eligible studies evaluating GSTT1 polymorphism in OPMD onset, involving 1798 OPMD patients and 3934 healthy controls. Overall, a significant association of OPMD susceptibility with GSTT1 null genotype was found with the random-effects model (pooled OR, 1.50; 95%CI, 1.01–2.22; $P_{heterogeneity}<0.00001$; Fig. 2B). Stratified analysis revealed a significantly increased risk in the OSF group (OR, 2.11; 95%CI, 1.26–3.53), but not in the OLK group (OR, 1.33; 95%CI, 0.79–2.23) and the non-specified OPMD group (OR, 1.38; 95%CI, 0.13–15.18).

There were 3 eligible studies on GSTM3 polymorphism in OPMD susceptibility, comprising 321 OPMD patients and 622 healthy controls. Overall, a marginally significant association of OPMD susceptibility with GSTM3 polymorphism was found with the fixed-effects model (pooled OR, 1.41; 95%CI, 1.00–1.98; $P_{heterogeneity} = 0.68$; Fig. 2C). Besides, there were 6 eligible studies investigated GSTP1 polymorphism in OPMD susceptibility, including 841 OPMD patients and 2043 healthy controls. No significant association was found with the fixed-effects model (pooled OR, 0.87; 95%CI, 0.74–1.03; $P_{heterogeneity} = 0.24$, $I^2 = 26$ %; Fig. 2D). Publication bias was evident for GSTM1 and GSTT1 ($P < 0.05$, Egger's test; Figure S2C, F), but not GSTM3 and GSTP1 polymorphisms ($P > 0.05$, Egger's test; Figure S2D, E).

Discussion

It is well-known that the complex interaction between genetic and environmental factors can affect individual susceptibility to oral cancer and precancer, which pose a significant public health challenge, particularly in South/Southeast Asian regions including India, Taiwan and mainland of China. The use of tobacco, alcohol, betel quid are well-established risk factors in oral carcinogenesis, yet the precise molecular mechanisms underlying genetic susceptibility remain incompletely characterized.[5] The compounds of first-level carcinogens require biotransformation and detoxification when they irritate the oral mucosa. The

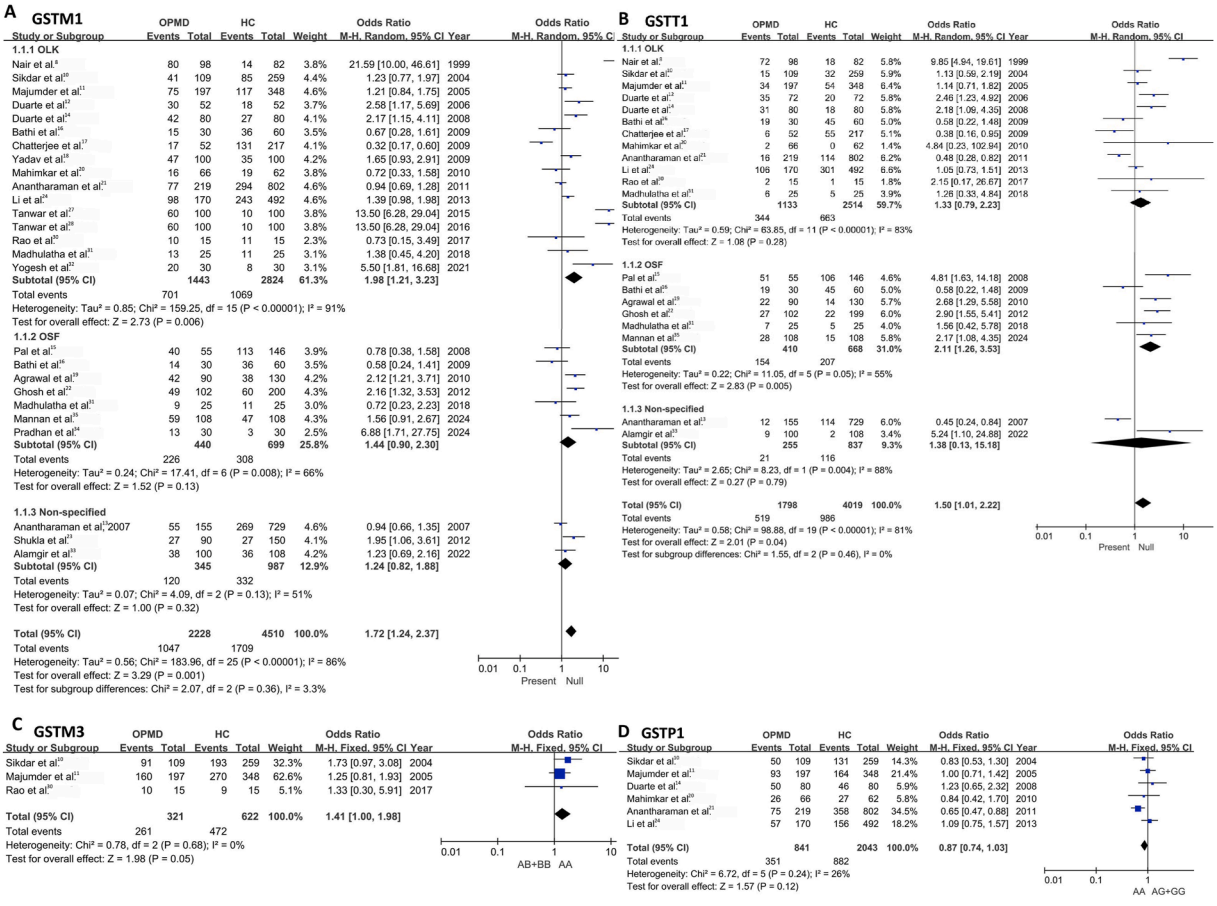

Figure 2 Forest plots of meta-analysis of genetic polymorphisms in Part II carcinogen metabolizing enzymes and oral potentially malignant disorders (OPMD) compared to healthy control. **(A)** GSTM1, **(B)** GSTT1 (**C**) GSTM3, (**D**) GSTP1. CI, confidence interval. OLK, oral leukoplakia. OSF, oral submucous fibrosis.

environment—gene interaction in carcinogenesis is reflected by Phase I (e.g. CYP1A1, CYP2E1) and Phase II (e.g. GSTM1, GSTM3, GSTT1 and GSTP1) enzymes that are related to the carcinogen metabolism.[3,4] In the previous meta-analyses, both GSTM1 and GSTT1 null polymorphisms were reported to be significantly increased the risk of OLK and OSF, whereas the GSTP1 polymorphism does not contribute to the development of OLK.[6,7]

This study for the first time identified all eligible studies to draw a more precise estimation of the genetic associations between SNPs in these 6 enzymes and OPMD onset in a single meta-analysis, because the results of these previous studies were conflicting.[8—35] This pooled-analysis provided a more accurate estimation of the association between SNPs in carcinogen metabolism enzymes and OPMD onset compared with individual study. We found that SNPs in CYP2E1 PstI variant, GSTM1, GSTM3 and GSTT1 were significantly associated with an increased risk of general OPMD, indicating these SNPs may be risk factors of OPMD. As for subtypes of OPMD, GSTM1 null polymorphism was significantly increased the risk of OLK and GSTT1 null polymorphism significantly increased the risk of OSF. Statistically, the two subgroups were of more evidently significant differences. These findings provide evidence that GSTM1 and GSTT1 null polymorphism significantly contribute to the development of OLK and OSF, respectively. These polymorphisms may reduce the capacity of detoxifying chemical carcinogens, leading to individuals in susceptibility to OPMD.

Although the efforts in performing a comprehensive analysis, certain limitations need to be addressed in this study. The number of eligible studies available with the sample size of most studies were small. The effect of the confounding factors, such as whether heath controls with or without areca nut chewing habit, the habit and duration of areca chewing, tobacco and alcohol use, were not estimated because of data unavailable in most studies (Table S2). Besides, the evidence of heterogeneity was observed in some genetic models possibly owing to methodological diversity in different studies. The negative results of CYP1A1, CYP2E1 RsaI or GSTP1 in OPMD onset analysis may be biased. This could be attributed to the relatively limited sample size, constrained geographic distribution and restricted ethnic diversity, particularly the fact that the majority of participants originated from India, may have introduced potential biases in the analysis. Furthermore, variations in lifestyle and external environmental factors among different populations may influence OPMD onset. Therefore, more well-designed studies with larger sample size and multiple ethnic groups, such as Taiwan and mainland of China, are needed to consolidate the findings.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2025.09.010.

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