**BMP4 rs17563 polymorphism and nonsyndromic cleft lip with or without cleft palate**

A meta-analysis

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**Abstract**

**Background:** Previous studies have investigated the relationship between human bone morphogenetic protein 4 gene (BMP4) rs17563 polymorphism and nonsyndromic cleft lip with or without cleft palate (NSCL/P). However, the results remained inconsistent. Therefore, we conducted a meta-analysis to assess the effect of BMP4 rs17563 polymorphism on NSCL/P.

**Methods:** Electronic searches in 5 databases were conducted to select all eligible studies up to March 2017. Odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were calculated to estimate the association. Sensitivity analysis was performed to evaluate the results stability by excluding each study in turn. Publication bias was assessed by Begg funnel plots and Egger test.

**Results:** A total of 11 case–control studies were included in the meta-analysis. The pooled frequency of the minor allele C for BMP4 rs17563 was lower in Asians (pooled frequency = 0.33, 95% CI: 0.29–0.37) than in Brazilian population (pooled frequency = 0.47, 95% CI: 0.40–0.54). The overall results showed no significant association of BMP4 rs17563 polymorphism with NSCL/P risk. However, the results turned out to be different when stratified by ethnicity. BMP4 rs17563 polymorphism was associated with a higher risk of NSCL/P among Asian ethnicity (C vs T: OR = 1.33, 95% CI: 1.02–1.73; CC vs TT: OR = 2.10, 95% CI: 1.28–3.43; CC vs TT + TC: OR = 2.16, 95% CI: 1.34–3.47) and among Caucasian population (TC vs TT: OR = 3.36, 95% CI: 2.03–5.54; TC + CC vs TT: OR = 3.71, 95% CI: 2.43–5.69). Among Brazilian population, BMP4 rs17563 polymorphism exerted a significantly protective effect on NSCL/P (C vs T: OR = 0.70, 95% CI: 0.58–0.84; CC vs TT: OR = 0.54, 95% CI: 0.33–0.88; TC vs TT: OR = 0.55, 95% CI: 0.44–0.69; TC + CC vs TT: OR = 0.56, 95% CI: 0.45–0.69).

**Conclusion:** The results suggest that the C allele of BMP4 rs17563 may be a risk factor for NSCL/P among Asians and Caucasians, and may be a protective factor for NSCL/P in Brazilian population. Future large-sample studies with appropriate designs among specific populations are warranted to evaluate the association.

**Abbreviations:** BMP4 = bone morphogenetic protein 4 gene, CIs = confidence intervals, HWE = Hardy–Weinberg equilibrium, MAF = minor allele frequency, NSCL/P = nonsyndromic cleft lip with or without cleft palate, ORs = odds ratios, SNPs = single nucleotide polymorphisms.

**Keywords:** BMP4, meta-analysis, nonsyndromic cleft lip with or without cleft palate, polymorphism, rs17563

1. Introduction

Nonsyndromic cleft lip with or without cleft palate (NSCL/P) is among the most common human congenital abnormalities worldwide. The live-birth prevalence of NSCL/P varied by geographic origin and ethnic groups, with 1/500 in Asians and American Indians, 1/1000 in European populations, and 1/2500 in African descent.\(^[1]\) NSCL/P can cause poor health outcomes because of the effects on speaking, feeding, hearing, appearance, and social integration. Although rehabilitation can be achieved to various degrees through surgery, dental treatment, and psychosocial intervention, NSCL/P inevitably poses a great burden to the families and society.\(^[2]\)

It has been suggested that both genetic predisposition and environmental exposures may contribute to the occurrence of NSCL/P. However, the molecular mechanisms remain poorly understood. Several potentially causal genes for NSCL/P have been identified over the past years, including TGF-\(\alpha\), IRF6, MTHFR, and MSX1.\(^{[3–6]}\)

The bone morphogenetic protein 4 gene (BMP4) is among the strong candidate genes for NSCL/P risk.\(^{[7]}\) In a BMP4 knockout...
mouse model, a CL/P phenotype was observed in embryos, indicating a role for the BMP signal pathway in lip and palate fusion. Animal studies also showed that chick embryos deficient in BMP4 exhibited craniofacial malformations, indicating the importance of BMP4 for craniofacial development. Moreover, BMP4 overexpression was observed in maxillary prominence of mouse embryo, which suggested an important function of BMP4 in mediating lip fusion.

The BMP4 T538C (rs17563) polymorphism is among the most functional single nucleotide polymorphisms (SNPs) in BMP4. The T→C sequence variation at 538 nucleotide position results in an amino acid change of Val/Ala (V152A) in the polypeptide. Several studies have focused on the effect of BMP4 rs17563 polymorphism on NSCL/P risk among humans, and their results were later summarized by a meta-analysis in 2014. However, in this previous meta-analysis, the number of included publications is limited (only 6) and the association among ethnic groups other than Chinese and Brazilian populations remains unknown. Moreover, more relevant human genetic association studies have been published among different populations since then, and the association results are not consistent. We, therefore, conducted an updated meta-analysis to assess the association between BMP4 rs17563 polymorphism and NSCL/P risk. The allele frequencies of BMP4 rs17563 among groups were also pooled in the current meta-analysis, which, to our knowledge, have not been investigated before.

2. Methods

2.1. Literature search strategy

Electronic searches in the PubMed, Embase, China National Knowledge Infrastructure, Wanfang, and China Biology Medicine databases were conducted up to March 2017. The following search terms were used: (“cleft lip” or “cleft palate” or “orofacial cleft” or “oral cleft”) and (“BMP4” or “bone morphogenetic protein 4”). The reference lists from reviews and retrieved studies were also scanned to find potential publications. Only articles in English or Chinese were included.

2.2. Eligibility criteria

Two reviewers (Y-HL and JY) independently excluded irrelevant studies by scanning all titles and abstracts of the retrieved articles, and they further independently read the full texts to select articles that met the eligibility criteria. Discrepancies were resolved by discussion with the third reviewer (ZZ). A study was included if it met the following inclusion criteria: case–control or cohort design; the outcome of interest was NSCL/P; the studied polymorphisms included BMP4 rs17563; sufficient data of genotype distributions to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). Articles without sufficient data of genotype distributions were excluded if authors did not provide information after 3 contacts. Animal studies and reviews were not included. Case-only and family-based studies were also removed. If multiple articles with similar or overlapped data were present, only the study with the most comprehensive information, such as the largest population or the longest study period, was included.

2.3. Data extraction

Data extraction was conducted independently by 2 reviewers (Y-HL and JY) through a standardized form. The following information was extracted from the included studies: first author’s surname, publication year, study type, study country, ethnicity, source of controls, sample size, genotyping method, and the genotype distributions in cases and controls. Disagreements between the 2 reviewers were settled by discussion with the third reviewer (DH).

2.4. Statistical analysis

The Hardy–Weinberg equilibrium (HWE) in the control group was calculated by Chi-square test, and P < .05 was considered as a significant deviation from HWE. The allele frequencies were assessed in each study, and pooled separately by ethnicity and disease groups. The strength of the association between BMP4 rs17563 polymorphism and NSCL/P was evaluated by crude ORs with 95% CIs under the following 3 genetic models: the allele model (C vs T), the homozygote model (CC vs TT), the heterozygote model (TC vs TT), the dominant model (TC+CC vs TT), and the recessive model (CC vs TT+TC). The significance of the pooled OR was determined by the Z test, with P < .05 regarded statistically significant. Heterogeneity across studies was assessed using both the Cochrane Q test and I² statistic. P < .1 or I² > 50% was suggestive of statistically significant heterogeneity. A random-effects model (DerSimonian and Laird method) was used when significant heterogeneity existed; otherwise, a fixed-effects model (Mantel–Haenszel method) was applied.

Subgroup analysis was conducted according to ethnicity, source of controls, and genotyping method. Sensitivity analysis was performed to evaluate the results stability by excluding each study in turn. In addition, publication bias was assessed by Begg funnel plots and Egger test at the P < .05 level of significance. All statistical analyses were conducted using STATA version 12.0 (Stata Corp, College Station, TX).

3. Results

3.1. Study characteristics

The flow chart of study selection is displayed in Fig. 1. Among the 68 citations retrieved from the electronic databases, 14 had the potential to be included after screening the titles or abstracts. Three articles of these were further excluded after reviewing the full texts because 2 articles did not investigate the BMP4 rs17563 mutation and one study did not provide sufficient data even after our 3 contacts. One study by de Araujo et al had insufficient data but the author provided additional data after our request. Thus, a total of 11 eligible publications were finally included in the present meta-analysis. The characteristics of the included studies are presented in Table 1. Of these studies, seven were hospital-based case–control designs, and 4 were population-based case–control designs. There were 6 studies conducted in Asians, 2 in Caucasians, and 3 in mixed population. The mixed population in the present study refers to the Brazilian population, which include European, African, Asian, American Indian, and their mixed descendants. Two genotyping methods including polymerase chain reaction—restriction fragment length polymorphism and TaqMan were utilized in the studies. The included studies had a total of 1633 cases and 1992 controls. The genotype distribution in the control group was consistent with HWE in all studies except for one.
0.33 (95% CI: 0.29–0.37) in Asians, 0.34 (95% CI: 0.17–0.51) in Caucasians, and 0.47 (95% CI: 0.40–0.54) in mixed population (Table 2), indicating a lower MAF C in Asians than in mixed population among normal people. The pooled MAF of the C allele in NSCL/P group were 0.40 (95% CI: 0.33–0.47) in Asians, 0.55 (95% CI: 0.46–0.63) in Caucasians, and 0.37 (95% CI: 0.34–0.40) in mixed population (Table 2), which suggested a higher MAF C in Caucasians than in mixed population among NSCL/P patients.

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

| First author, year | Country | Ethnicity | Source of controls | Genotyping method | Study size | Genotype distribution (TT/TC/CC) | P for HWE in controls |
|--------------------|---------|-----------|--------------------|-------------------|------------|---------------------------------|----------------------|
| Lin et al          | China   | Asian     | Hospital-based     | PCR-RFLP          | 200/200    | 74/90/36, 89/94/17              | .26                  |
| Lu[20]             | China   | Asian     | Hospital-based     | PCR-RFLP          | 40/40      | 12/17/11, 10/25/5               | .09                  |
| Araujo et al[21]   | Brazil  | Mixed     | Population-based   | PCR-RFLP          | 123/246    | 49/53/21, 52/130/46             | .35                  |
| Wang et al[22]     | China   | Asian     | Hospital-based     | PCR-RFLP          | 65/65      | 21/32/12, 32/28/5               | .74                  |
| Antunes et al[23]  | Brazil  | Mixed     | Hospital-based     | TaqMan            | 382/436    | 176/147/59, 159/224/62          | .14                  |
| Hao[24]            | China   | Asian     | Hospital-based     | PCR-RFLP          | 165/52     | 91/61/13, 20/27/5               | .34                  |
| You et al[25]      | China   | Asian     | Population-based   | PCR-RFLP          | 116/123    | 40/40/36, 46/66/11              | .06                  |
| Jin et al[26]      | China   | Asian     | Hospital-based     | PCR-RFLP          | 154/190    | 66/70/18, 104/69/17             | .26                  |
| Savitha et al[27]  | India   | Caucasian | Hospital-based     | PCR-RFLP          | 100/100    | 32/18/50, 68/13/10              | <.001                |
| de Araujo et al[28] | Brazil  | Mixed     | Population-based   | TaqMan            | 182/354    | 70/81/31, 95/173/86             | .68                  |
| Saket et al[29]    | Iran    | Caucasian | Population-based   | PCR-RFLP          | 106/186    | 16/74/16, 65/83/38              | .23                  |

HWE = Hardy–Weinberg equilibrium, PCR-RFLP = polymerase chain reaction–restriction fragment length polymorphism.
The overall results suggested no association of BMP4 rs17563 polymorphism with NSCL/P risk, and significant heterogeneity existed in all genetic models (Table 3). However, the results turned out to be different when stratified by ethnicity. Among Asian ethnicity, BMP4 rs17563 polymorphism was associated with a higher risk of NSCL/P (C vs T: OR = 1.33, 95% CI: 1.02–1.73; CC vs TT: OR = 2.10, 95% CI: 1.28–3.43; CC vs TT + TC: OR = 2.16, 95% CI: 1.34–3.47), and no significant heterogeneity was observed under the homozygote model (I² = 42.2%, P = .12). Among Caucasian population, BMP4 rs17563 polymorphism may contribute to an increased risk of NSCL/P (TC vs TT: OR = 3.36, 95% CI: 2.03–5.54, Fig. 2; TC+CC vs TT: OR = 3.71, 95% CI: 2.43–5.69), and heterogeneity was absent under the heterozygote model (I² = 0%, P = .70) and dominant model (I² = 0%, P = .36). In contrast, among Brazilian population, BMP4 rs17563 polymorphism exerted a significantly protective effect on NSCL/P (C vs T: OR = 0.70, 95% CI: 0.58–0.84; CC vs TT: OR = 0.54, 95% CI: 0.33–0.85; TC vs TT: OR = 0.55, 95% CI: 0.44–0.69, Fig. 2; TC+CC vs TT: OR = 0.56, 95% CI: 0.45–0.69), and heterogeneity was not statistically significant under the heterozygote model (I² = 39.9%, P = .19), heterozygote model (I² = 0%, P = .51), or dominant model (I² = 12.0%, P = .32). Subgroup analysis by source of controls yielded a significant association in hospital-based studies under the recessive model (CC vs TT+TC: OR = 1.87, 95% CI: 1.17–3.00), while no associations were observed in population-based studies under any genetic models. When stratified by genotyping type, significant protective effect of BMP4 rs17563 polymorphism on NSCL/P was found in TaqMan subgroup (C vs T: OR = 0.75, 95% CI: 0.64–0.88; TC vs TT: OR = 0.59, 95% CI: 0.46–0.75; TC+CC vs TT: OR = 0.60, 95% CI: 0.48–0.76), and heterogeneity was absent under the 3 genetic models (all I² = 0%). In fact, these 2 studies using TaqMan genotyping method were both conducted in Brazilian population.

### 3.3. Sensitivity analysis

The association between BMP4 rs17563 polymorphism and NSCL/P risk did not materially alter after excluding each study in turn under any genetic models. Although the genotype distribution in one included study was not in HWE, the pooled ORs did not qualitatively change when it was removed. The sensitivity analysis revealed the statistical robustness of our results.

| First author, Year | No. | C allele | T allele | No. | C allele | T allele |
|--------------------|-----|---------|---------|-----|---------|---------|
| **Source of controls** | | | | | | |
| Hospital-based | 130 | 80 | 14 | 60 | 30 | 90 |
| Population-based | 146 | 92 | 54 | 58 | 30 | 28 |
| **Genotyping method** | | | | | | |
| PCR-FRAP | 130 | 80 | 14 | 60 | 30 | 90 |
| TaqMan | 146 | 92 | 54 | 58 | 30 | 28 |

**Table 3**

| Source of controls | No. | C allele | T allele | No. | C allele | T allele |
|--------------------|-----|---------|---------|-----|---------|---------|
| **Ethnicity** | | | | | | |
| Asian | 130 | 80 | 14 | 60 | 30 | 90 |
| Caucasian | 146 | 92 | 54 | 58 | 30 | 28 |
| **Mixed** | | | | | | |
| Overall | 130 | 80 | 14 | 60 | 30 | 90 |
| **Subgroup** | | | | | | |
| Hospital-based | 130 | 80 | 14 | 60 | 30 | 90 |
| Population-based | 146 | 92 | 54 | 58 | 30 | 28 |

**Table 2**

**Table 2**

Estimated pooled frequencies of minor and major alleles for BMP4 rs17563 by ethnicity and disease groups in the meta-analysis.

| First author, Year | No. | C allele | T allele | No. | C allele | T allele |
|--------------------|-----|---------|---------|-----|---------|---------|
| **Source of controls** | | | | | | |
| Asian | 130 | 80 | 14 | 60 | 30 | 90 |
| Caucasian | 146 | 92 | 54 | 58 | 30 | 28 |
| **Mixed** | | | | | | |
| Overall | 130 | 80 | 14 | 60 | 30 | 90 |
| **Subgroup** | | | | | | |
| Hospital-based | 130 | 80 | 14 | 60 | 30 | 90 |
| Population-based | 146 | 92 | 54 | 58 | 30 | 28 |
3.4. Publication bias

No publication bias was detected for the association of BMP4 rs17563 polymorphisms with NSCL/P risk according to the Egger test ($P = .14$ for C vs T, $P = .21$ for CC vs TT, $P = .22$ for TC vs TT, $P = .21$ for TC+CC vs TT, and $P = .14$ for CC vs TT+TC), and the funnel plots seemed no evidence of obviously asymmetrical (Fig. 3 for the heterozygote model).

4. Discussion

In the present study, we conducted an updated meta-analysis to assess the effect of BMP4 rs17563 polymorphism on NSCL/P risk. The MAF of the C allele for BMP4 rs17563 was lower in Asians than in Brazilian population. The pooled results showed no association of BMP4 rs17563 polymorphism with NSCL/P risk. However, the subgroup analysis by ethnicity suggested that the C allele of BMP4 rs17563 may be a risk factor for NSCL/P in Asians and Caucasians, while a protective effect of the BMP4 rs17563 C allele on NSCL/P was found in Brazilian population.

Our overall results and the results of subgroup analysis on Asians and Brazilian population are consistent with the previous meta-analysis, which included a total of 6 studies conducted in Chinese and Brazilian populations.[11] We confirmed the previous findings by expanding the number of included studies to 11 with a larger sample size. Not only was the effect of BMP4 rs17563 polymorphism on NSCL/P among Caucasians evaluated, but also the pooled allele frequencies among groups were additionally provided in the current meta-analysis.

Development of the lip and palate occurs in early pregnancy and entails a complex process of cell growth, differentiation, migration, and apoptosis.[1] Evidence suggests that both genetic and nongenetic factors are involved in the etiology of NSCL/P. Environmental risk factors, maternal smoking, alcohol drinking, and poor nutrition during the periconceptional period may increase the risk of NSCL/P.[1] Genetic studies of NSCL/P have identified several causative genes including TGF-α, IRF6, MTHFR, and MSX1, although the results differ among populations. Moreover, gene-environment interactions have been investigated as important factors for NSCL/P etiology. For example, the study by Lin et al reported a synergistic effect between BMP4 rs17563 variation and maternal passive smoking.

BMP4, a member of the transforming growth factor-beta superfamily, has distinct functions in embryonic development, including craniofacial development.[9] The presence of a CL/P phenotype in BMP4 knockout mice revealed the role of BMP4 in lip and palate fusion.[8] Chick embryos deficient in BMP4 also exhibited craniofacial malformations.[9] Moreover, experimental research showed that BMP4 could be overexpressed in the maxillary prominence,[10] which formed the lateral parts of the upper lip and the secondary palate.[27] These studies suggest that BMP4 is a strong candidate gene for NSCL/P.
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