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The Role of PAX9 and MSX1 Variants in Non-Syndromic Tooth Agenesis

Finna[1], Ameta Primasari[2*], Sry Suryani Widjaja[3], Thantrira Porntaveetus[4], Ervina Sofyanti[5]

[1]*Faculty of Dentistry, Universitas Sumatera Utara, Medan, 20155 Indonesia*
[2]*Department of Oral Biology, Faculty of Dentistry, Universitas Sumatera Utara, Medan, 20155 Indonesia*
[3]*Department of Biochemistry, Faculty of Medicine, Universitas Sumatera Utara, Medan, 20155 Indonesia*
[4]*Center of Excellence in Genomics and Precision Dentistry, Department of Physiology, Faculty of Dentistry, Chulalongkorn University, Bangkok 10330, Thailand*
[5]*Department of Orthodontics, Faculty of Dentistry, Universitas Sumatera Utara, Medan, 20155 Indonesia*

[*]Corresponding Author: ameta.primasari@usu.ac.id

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ABSTRACT

Non-syndromic tooth agenesis (NSTA) is the congenital absence of teeth without systemic involvement. Genetic polymorphisms in *PAX9* and *MSX1* are implicated in tooth development, but results vary across populations. Therefore, this study aims to explore the role of *PAX9* c.-1031G>A and *MSX1* 671 T>C polymorphisms with NSTA in individuals from Medan. A total of 13 NSTA patients and 26 control were genotyped using PCR-restriction fragment length polymorphism (PCR-RFLP). The results showed that the AA genotype of *PAX9* was absent in NSTA cases but found in 26.92% of controls. The GG genotype was reported to be more common in 38.46% of cases, while the G allele was prevalent in 69.23%. These trends suggested a potential association, but it was not statistically significant. In this study, all patients carried the TT genotype for *MSX1*. These results show a possible role of *PAX9* polymorphisms in NSTA susceptibility and support the need for further studies in larger populations.

Keywords: Tooth Agenesis, Genetic, Polymorphism

ABSTRAK

Agenesis gigi non-sindromik adalah kondisi bawaan umum yang ditandai dengan tidak adanya gigi permanen tanpa keterlibatan sistemik. Polimorfisme genetik pada *PAX9* dan *MSX1* diduga berperan dalam perkembangan gigi, namun temuan ini bervariasi antar populasi. Penelitian ini mengeksplorasi peran varian genetik *PAX9* c.-1031G>A dan *MSX1* 671 T>C dalam kejadian agenesis gigi non-sindromik pada individu dari Medan. Sebanyak 13 pasien dengan agenesis gigi non-sindromik dan 26 subjek control dianalisis genotipenya menggunakan metode *PCR-restriction fragment length polymorphism* (PCR-RFLP). Genotipe AA pada *PAX9* tidak ditemukan pada kasus agenesis gigi non-sindromik, tetapi terdapat pada 26,92% kelompok kontrol, sementara genotipe GG lebih sering ditemukan pada kasus (38,46%). Alel G juga lebih dominan pada kasus (69,23%). Meskipun secara statistik tidak signifikan, tren ini menunjukkan adanya potensi hubungan. Sebaliknya, semua subjek memiliki genotipe TT untuk *MSX1*. Temuan ini mengindikasikan kemungkinan peran polimorfisme *PAX9* dalam kerentanan terhadap agenesis gigi non-sindromik dan mendukung perlunya penelitian lanjutan dengan populasi yang lebih besar.

Kata kunci: Agenesis Gigi, Genetik, Polimorfisme

1. Introduction

Non-syndromic tooth agenesis (NSTA) is a commonly encountered dental developmental disorder. It is characterized by the congenital lack of one or more permanent teeth (not including third molars) in the absence of systemic disorders. The classification of this condition depends on how many teeth are absent, and includes hypodontia, oligodontia, and anodontia [1,2]. This anomaly arises from disturbances in the initial phases of odontogenesis, particularly during the initiation and proliferation stages [2,3]. Several studies have shown that it is typically identified through a combination of clinical evaluation and radiographic imaging, which allows for the accurate assessment of missing teeth and developmental anomalies [3,4].

According to previous studies, NSTA poses both functional and aesthetic challenges for affected individuals. These include deep bite, spacing, excessive eruption of the opposite teeth, poor gingival contour, and chewing difficulty. Apart from the clinical impact, it often requires long-term and costly multidisciplinary treatment, such as orthodontic, prosthetic, and sometimes surgical interventions. These implications show the urgency of understanding the underlying causes to facilitate earlier diagnosis, preventive strategies, and more efficient treatment planning [5,6].

The prevalence of NSTA has been shown to vary across different populations. For example, a study conducted by Bozga et al. reported that 6.76% of the Bucharest population experienced tooth agenesis (TA) [7]. In addition, Yunus et al. found that among 532 individuals in Makassar city, 68.04%. 26.93%, and 5.21% had hypodontia, oligodontia, and anodontia, respectively [8]. The Makassar population is relatively homogenous and predominantly consists of Bugis-Makassar ethnic groups, while Medan is more heterogeneous, comprising Batak, Javanese, and Chinese ethnicities. The differences in genetic background and cultural diversity, along with population-specific environmental conditions, such as maternal health, nutrition, and healthcare access, may contribute to variations in the prevalence of TA. In addition, racial and ethnic characteristics can influence tooth development, including eruption timing, size, and crown morphology. Some groups may also be more susceptible to anomalies, such as retained primary teeth or delayed eruption of permanent teeth, which can further contribute to differences in the occurrence of TA across populations [9,10]. Despite the widespread nature of the condition, there are no studies on the prevalence of TA in the Medan population, showing the need for further exploration in the area.

The development of NSTA is influenced by both genetic and environmental factors, with genetic predisposition playing a more significant role. Several key genes have been reported to be involved in tooth development, including *PAX9* (Paired Box 9) and *MSX1* (Muscle Segment Homeobox 1), which are essential for craniofacial formation and tooth morphogenesis. These genes participate in essential signaling pathways that regulate the early stages of dental lamina formation. Mutations or polymorphisms that affect their function can disrupt the normal sequence of tooth development [3,11,12]. Environmental factors also contribute to the risk of NSTA, including intrauterine exposure to thalidomide, maternal smoking or alcohol use, infections such as rubella, trauma to the alveolar process, and cancer therapies (chemotherapy or head and neck radiation) [3,13].

Previous genetic studies have shown that there are associations between specific polymorphisms, including *PAX9* c.-1031G>A and *MSX1* 671T>C, with susceptibility to NSTA [14,15]. However, the results remain inconsistent across different ethnic populations due to various factors. The inconsistency may reflect differences in genetic backgrounds among populations, as previously discussed. It can also be caused by other factors, such as sample size and methodological limitations. The varying results show a critical gap in the literature, indicating the need for further population-specific genetic studies to clarify these relationships and improve the reliability of genetic markers for clinical use.

The majority of existing studies solely focus on non-Indonesian populations, leading to a lack of genetic data related to NSTA in Indonesian ethnic groups. Therefore, this case-control study aims to examine the association between *PAX9* c.-1031G>A and *MSX1* 671T>C polymorphisms and the risk of NSTA in individuals from Medan. The results of the study are expected to contribute to the existing body of knowledge on dental genetics and support the development of more accurate, population-based approaches for early detection and personalized treatment of NSTA.

2. Materials and Methods

This case-control study included 13 NSTA patients and 26 controls, conducted from September 2024 to March 2025. Participants were recruited and blood samples were obtained at Aviati Clinic in Padang Bulan, Medan, where diagnoses were confirmed through medical history and orthopantomograms. For those who no longer retained their previous radiographic records, orthopantomograms were obtained at Laboratorium Klinik Pramita, Medan. Genomic DNA was extracted, and polymorphism analyses were performed at the Integrated Laboratory of the Faculty of Medicine, Universitas Sumatera Utara. Approval from the appropriate institutional ethics committee was secured before the study commenced (Ethical Approval No. 223/KEPK/USU/2024), and informed consent was collected in writing from each participant.

Participants were recruited from the heterogeneous population of Medan, which included Batak, Javanese, and Chinese ethnic groups. The case group consisted of individuals aged 18 to 30 years who met the inclusion criteria, namely having at least 1 congenitally missing permanent tooth (excluding third molars), a history of prior treatment at the Dental and Oral Hospital of Universitas Sumatera Utara (RSGM USU), no previous tooth extraction or surgical intervention in the affected region, and no systemic disorders or oral pathologies. The control group consisted of healthy, unrelated individuals exhibiting a complete set of primary and permanent teeth, with no history of systemic conditions or oral health disorders.

This study workflow included patient recruitment, sample collection, DNA extraction, gene amplification, restriction enzyme digestion, electrophoresis, and statistical analysis. Genomic DNA used for single-nucleotide polymorphism (SNP) analysis was extracted from peripheral blood drawn into sterile EDTA tubes, using the Promega Wizard® Genomic DNA Purification Kit in accordance with the provided protocol. DNA concentration and purity were evaluated using a nanophotometer, and the samples were preserved at –20°C until further analysis.

Polymorphism analysis for both *PAX9* and *MSX1* genes was carried out using the restriction fragment length polymorphism (RFLP) technique. For *PAX9*, the method followed the protocol outlined by Peres et al., using the HaeIII restriction enzyme [16]. PCR was amplified using forward primer 5’-AGC CTG AAT CCT GTG TGC AC-3’ and reverse primer 5’-CTA ATC TAA AGT GTA CCG TAT GC-3’, generating a 202 base pair (bp) product. Each PCR reaction mixture included 12.5 µL PCR master mix, 1 µL of each primer, 7.5 µL nuclease-free water, and 3 µL of DNA template. The thermal cycling protocol included an initial denaturation step at 95°C for 5 minutes, 35 cycles of 95°C for 30 seconds (denaturation), 55°C for 30 seconds (annealing), and 72°C for 30 seconds (extension). This was followed by a final elongation step at 72°C for 5 minutes. The resulting PCR product was confirmed through 2% agarose gel electrophoresis. HaeIII digestion identified the -1031G allele as uncut, while the -1031A allele produced fragments of 176 bp and 26 bp.

For *MSX1* polymorphism analysis, RFLP method was applied following the protocol established by Reddy et al., using the Eco31I enzyme derived from *Escherichia coli* [14]. The primers used were *MSX1*ex2.2F (5’-AGAAGCAGTACCTGTCCATCG-3’) and *MSX1*ex2.2R (5’-AACCTCTCTGCCCTCAGTTTC-3’), amplifying a 448 bp DNA fragment. PCR amplification was carried out under similar conditions, making adjustments to the annealing temperature (59°C) and extension time (45 seconds). In addition, the thermal protocol included an initial denaturation at 95°C for 5 minutes, followed by 35 cycles of 95°C for 30 seconds, 59°C for 30 seconds, and 72°C for 45 seconds, ending with a final extension at 72°C for 5 minutes. The PCR amplicons were analyzed on a 2% agarose gel before proceeding with enzymatic digestion.

The collected data were analyzed using SPSS software version 22.0. Categorical variables were compared using the Chi-square test, with Fisher’s exact test was applied where applicable, particularly for small sample sizes. Results were tabulated, and a *p-value* below 0.05 was deemed statistically significant.

3. Results

This study comprised 13 NSTA individuals of varying ages and both genders, with an average and median age of 25, showing a younger skew. The mode, or most frequently occurring age, was also 25, with females making up the majority (8 of 13). Regarding TA severity, 46.15% had 1 missing tooth, 15.38% had 2, and 38.46% had 3 or more (Table 1). Incisors and premolars were the most frequently absent.

Table 1. Participants Characteristics and TA Patterns in NSTA

Subject Characteristics	N (%)
Gender	
Males	5 (38.46%)
Females	8 (61.54%)
Age category (in years)	
18-20	1 (7.69%)
21-25	7 (53.85%)
26-30	5 (38.46%)
Number of missing teeth	
1	6 (46.15%)
2	2 (15.38%)
3 or more	5 (38.46%)
Commonly missing teeth	
Upper lateral incisor	9 (28.12%)
Upper second premolar	3 (9.37%)
Lower lateral incisor	4 (12.5%)
Lower second premolar	5 (15.62%)
Lower first molar	3 (9.37%)
Others	8 (25%)

Table 2. Frequencies of genotypes and alleles for the *PAX9* c.-1031G>A variant

	NSTA Subjects		Control Subjects		*P-value*
	n	%	n	%	
AA	-	-	7	26.92%	0.063[a]
GA	8	61.53%	15	57.69%	
GG	5	38.46%	4	15.38%	
Allele A	8	30.77%	29	55.77%	0.054[b]
Allele G	18	69.23%	23	44.23%	

Notes: [a]Fisher's exact test. [b]Chi-squared test.

Table 3. Frequencies of genotypes and alleles for the *MSX1* 671 T>C variant

	NSTA Subjects		Control Subjects		*P-value*
	n	%	n	%	
TT	13	100%	26	100%	-
TC	-	-	-	-	
CC	-	-	-	-	
Allele T	26	100%	52	100%	-
Allele C	-	-	-	-	

Notes: All participants in both NSTA and control groups showed the TT genotype exclusively, with no observed C alleles. Due to the lack of genotypic variation, statistical comparison was not applicable, and a *p-value* could not be calculated.

Table 2 showed the frequencies of genotypes and alleles for the *PAX9* c.-1031G>A SNP in NSTA and control groups. The result did not attain statistical significance (Fisher's exact test, $P = 0.063$), but a discernible trend was observed. Interestingly, the AA genotype was completely absent among individuals with NSTA, yet present in 26.92% of the control group. Meanwhile, the GG genotype was more common in NSTA (38.46% vs. 15.38%).

The G allele was more dominant in NSTA (69.23%), while the A allele predominated in controls (55.77%), with a *p-value* of 0.054, falling just short of statistical significance. While these results did not surpass the conventional threshold for statistical significance, the distribution trends pointed toward a possible link between the -1031G allele and susceptibility to NSTA.

All participants in both the NSTA and control groups exhibited a homozygous wild-type TT genotype for the *MSX1* 671 T>C variant, with no TC or CC genotypes and no C alleles detected. Due to this lack of variation, statistical analysis was not possible. The absence of diversity suggested that further study with larger,

more diverse populations was needed to evaluate this variant's role, while no association with NSTA was observed.

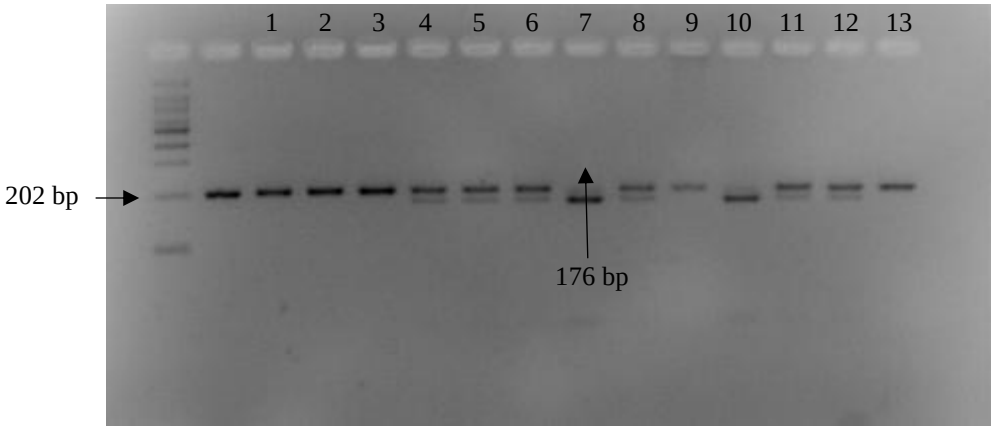

Figure 1. Analysis of *PAX9* c.-1031G>A polymorphism in NSTA samples using gel electrophoresis. The 202 bp PCR products were treated with the HaeIII restriction enzyme. Lanes 1–3, 9, and 13 display the homozygous GG genotype, whereas lanes 4–8 and 10–12 exhibit the heterozygous GA genotype.

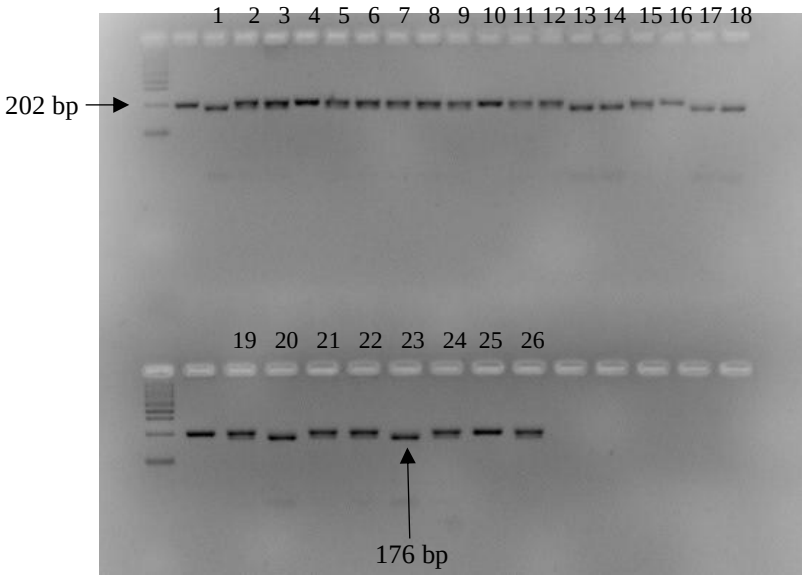

Figure 2. Analysis of the *PAX9* c.-1031G>A polymorphism in control group samples using gel electrophoresis. The 202 bp PCR products were digested with the HaeIII restriction enzyme. Lanes 1, 13–14, 17–18, and 20 show the homozygous AA genotype, while lanes 4, 10, 16, and 25 show the homozygous GG genotype. The heterozygous GA genotype is observed in lanes 2–3, 5–9, 11–12, 15, 19, 21–22, 24, and 26.

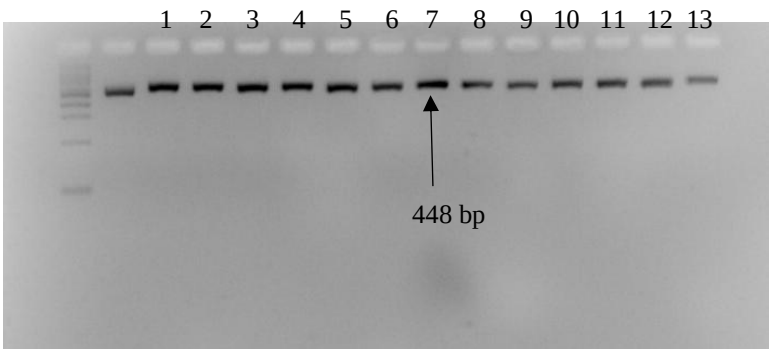

Figure 3. Analysis of *MSX1* 671 T>C polymorphism in NSTA samples using gel electrophoresis. The 448 bp PCR products were treated with The Eco31l restriction enzyme. All lanes exhibit the homozygous wild-type genotype (TT).

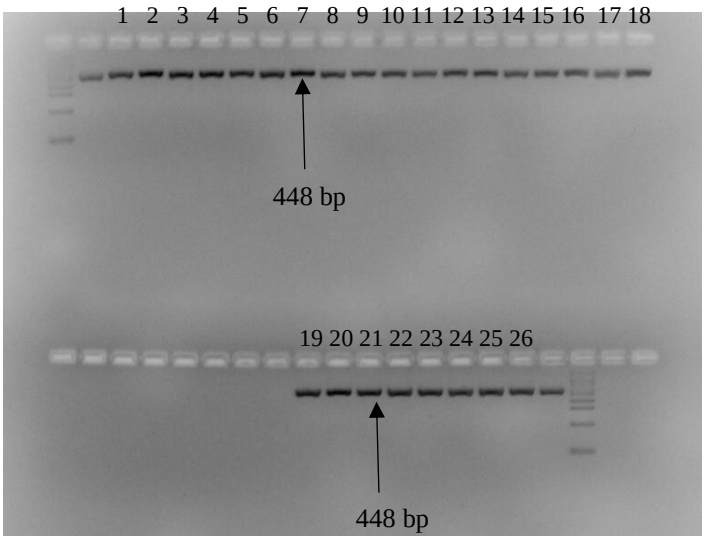

Figure 4. Analysis of the *MSX1* 671 T>C polymorphism in control group samples using gel electrophoresis. The 448 bp PCR products were treated with the Eco31l restriction enzyme. All lanes exhibit the homozygous wild-type genotype (TT).

4. Discussion

A total of 13 individuals with NSTA participated in this study, with a mean age of 25 years, and most were aged 21-25, suggesting a greater occurrence of NSTA in younger people. Yunus et al. noted that agenesis was most common in adults aged 26 to 45 [8]. Females accounted for 61.54% of the participants, which was consistent with the observations reported by Salvi et al. and Yunus et al., who also documented a higher incidence of agenesis in females [8,17]. This could be because females generally seek dental treatment more frequently than males, which influenced the sample composition [18]. Furthermore, aesthetic concerns explained why females are more likely to seek care, particularly in visible cases, while males often prioritize treatment when functional issues arise [19].

As summarized in Table 1, the most frequent agenesis pattern in this study included the absence of a single tooth (46.15%), with upper lateral incisors being the most commonly missing teeth. This differed from results reported by Salvi et al., Boutahari et al., and Biedziak et al., who observed the second premolars to be the most frequently absent, with the lateral incisors following [17,20,21]. As summarized by Cavare et al., multiple studies have proposed that the absence of distally located teeth, particularly lateral incisors and second premolars, reflected a continuing evolutionary trend in humans toward fewer teeth and smaller jaws. Such discrepancies reflected population-specific variation. Agenesis of anterior teeth, particularly lateral incisors, carried greater esthetic and functional implications than posterior agenesis, emphasizing the need for early treatment planning in affected patients [19].

Tooth development involved tightly regulated gene interactions, with *PAX9* and *MSX1* playing major roles during the bud and cap stages. *PAX9* and *MSX1* homeobox domains also contributed to odontogenesis, and loss-of-function mutations in either gene resulted in NSTA. Both genes exhibited expression in mesenchymal tissues required in tooth development, and their disruption could lead to developmental arrest [22–24].

While most studies concentrated on coding mutations, recent studies have begun to explore the impact of common polymorphisms, particularly those in non-coding regulatory regions. In this study, the association between *PAX9* c.-1031G>A and *MSX1* 671 T>C polymorphisms, as well as NSTA in the Medan population, was investigated.

For the *PAX9* c.-1031G>A variant (Table 2), the GG genotype and G allele were more frequent among NSTA cases than controls, while the AA genotype was absent in all cases but present in 26.92% of controls. Although the association did not reach statistical significance, the *p-values* for both genotype ($p = 0.063$) and allele distribution ($p = 0.054$) approached the threshold of significance, suggesting that a larger sample size

could have yielded clearer results. The absence of the AA genotype in the affected group showed a potential protective effect of the A allele, which was also suggested in other populations. Moreover, the trend observed in this study was consistent with results from Jordanian and Turkish cohorts, where the GG genotype and G allele were reported at higher frequencies among individuals with agenesis [15,25]. Given the established role of *PAX9* in regulating the bud-to-cap transition and its interaction with odontogenic signaling pathways such as *BMP4*, *MSX1*, and *FGF* signaling, even modest genetic variations at this locus could alter tooth development and contribute to susceptibility to NSTA [26]. The PCR-RFLP analysis presented in Figures 1 to 2 further confirmed these genotype distributions, strengthening the reliability of the observed trends.

Analysis of the *MSX1* 671T>C variant (Table 3) showed no genotypic or allelic variation, with all participants carrying the TT genotype. The electrophoresis images in Figures 3 to 4 corroborated these results, showing uniform wild-type genotypes in both NSTA and control groups. This lack of variation prevented further statistical analysis and suggested that the C allele was rare or absent in the Medan population. By comparison, studies from Raichur and European cohorts reported significant associations with *MSX1* variants, showing potential population-specific differences in genetic susceptibility [14,27]. The negative result in this study did not necessarily exclude the role of *MSX1*, but instead emphasized the importance of evaluating additional polymorphic sites, particularly in regulatory or coding regions not covered by the present assay. Broader approaches, such as next-generation sequencing, could be required to capture a more comprehensive picture of *MSX1* variation in Indonesian populations.

Participants in this study did not originate from a single ethnic background, but rather from the heterogeneous population of Medan, which included Batak, Javanese, and Chinese groups. Such heterogeneity could reduce the ability to detect genetic associations, specifically in small cohorts, because population substructure could mask or dilute potential signals. This differed from studies conducted in more homogenous populations, such as Jordanian or Turkish cohorts, where clearer associations between *PAX9* or *MSX1* variants and NSTA were reported [15,25]. Therefore, the lack of statistically significant results in this study partly reflected underlying genetic diversity among participants rather than the absence of a biological effect.

Collectively, the data presented in Tables 1 to 3 and Figures 1 to 4 reinforced the potential role of *PAX9* polymorphisms in NSTA susceptibility, while suggesting a limited contribution of the *MSX1* 671 T>C variant in this cohort. The observed genotype and allele frequency trends, although not statistically significant, were consistent with the biological importance of *PAX9* in tooth development. These results emphasized the need for larger, population-specific studies in Indonesia to account for genetic heterogeneity and to better clarify the roles of *PAX9* and *MSX1* variants in NSTA.

TA represented a clinical and genetic challenge that required early recognition and comprehensive management. Timely diagnosis was essential not only for guiding facial growth and occlusion but also for minimizing negative impacts on patients' self-esteem and quality of life. Management typically included a multidisciplinary approach, integrating pediatric dentistry, orthodontics, prosthodontics, and sometimes surgery to achieve optimal rehabilitation [28–31]. From a genetic perspective, this study provided preliminary evidence that *PAX9* polymorphisms contributed to NSTA susceptibility in Indonesian populations, while *MSX1* variants appeared less relevant in this cohort. Although the results did not reach statistical significance, the importance of incorporating genetic considerations into early detection and personalized treatment planning tailored to diverse population backgrounds was emphasized. However, these results must be interpreted with caution, as the limited sample size and ethnic variability reduced the statistical power to detect significant associations. Larger-scale studies with broader coverage of Indonesian ethnic groups were essential to validate these associations and ultimately support the development of precision dentistry in the region.

5. Conclusion

In conclusion, the roles of *PAX9* c.-1031G>A and *MSX1* 671 T>C in NSTA susceptibility are examined. Although *PAX9* shows a trend toward association, particularly the absence of the AA genotype in NSTA cases, statistical significance has not been reached. The *MSX1* variant shows no C alleles in this cohort, preventing meaningful analysis and emphasizing the need for more genetically diverse populations in future studies. Given the variability in previous results across populations, further study with larger, diverse cohorts is essential to clarify the roles of these genes in TA.

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7. Conflict of Interest

The authors state that there are no disclosures or conflicts of interest connected to this study.

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