牙颌面畸形专题

伴有 *PAX9* 突变非综合征型先天缺牙患者的牙颌面表型研究

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［摘要］**目的**·评估配对盒基因9（paired box gene 9，*PAX9*）突变非综合征型先天缺牙（non-syndromic tooth agenesis，NSTA）患者的牙颌面表型。**方法**·对2016年1月—2023年12月于上海交通大学医学院附属第九人民医院口腔第二门诊部就诊的NSTA患者进行全外显子组测序，筛查*PAX9*突变患者。对筛查到的患者采用曲面体层摄影片评估缺牙的位置和数目，采用X射线头影测量评估患者的牙颌面畸形情况。**结果**·7例*PAX9*突变的NSTA患者纳入研究，男性3例（42.9%），女性4例（57.1%）。患者首诊年龄7~31岁，平均（19.7±8.0）岁。7例患者均携带*PAX9*杂合突变，其中4例为错义突变，3例为移码突变。平均缺失恒牙（15.9±2.9）颗，上颌缺失数［（9.6±2.6）颗］略多于下颌［（6.3±2.4）颗］（*P*=0.030）。上颌第二磨牙（100.0%）、上颌尖牙（85.7%）、下颌第二前磨牙（85.7%）为最常见的缺失位点，下颌侧切牙（14.3%）、下颌尖牙（14.3%）为最少缺失的位点。移码突变的患者缺牙数［（18.3±2.1）颗］多于错义突变［（14.0±1.8）颗］（*P*=0.032）。X射线头影测量结果显示：*PAX9*突变成年患者上牙槽座角（angle sella-nasion-subspinale，SNA）、颌凸角（angle nasion-subspinale-subspinale-porion，NA-APo）和前颅底长度（sella-nasion，S-N）均明显小于正常参考范围，提示上颌后缩，前颅底矢状向发育不足；面角（frankfort horizontal plane-nasion-porion，FH-NPo）大于参考值、Y轴角（Y axis）小于参考值，提示下颌前伸；上/下牙槽座角（angle subspinale-nasion-supramental，ANB）小于参考值，提示骨性Ⅲ类错𬌗畸形；上中切牙角（angle upper central incisor-nasion-subspinale，angle U1-NA）大于参考值，提示上中切牙唇倾；下中切牙-下颌平面角（angle lower central incisor-mandibular plane，IMPA）、下中切牙凸度（lower central incisor-nasion-supramental，L1-NB）小于参考值，提示下中切牙舌倾，上下前牙反𬌗倾向。**结论**·较为全面地报道了*PAX9*突变NSTA患者的牙颌面表型，有利于进一步理解*PAX9*在人类颌面部发育中的作用。

［关键词］配对盒基因9；牙颌面畸形；X射线头影测量；非综合征型先天缺牙；骨性Ⅲ类错𬌗畸形
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Dentofacial phenotype of non-syndromic tooth agenesis patients with *PAX9* mutation

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[**Abstract**] **Objective**·To evaluate the dentofacial phenotype in non-syndromic tooth agenesis (NSTA) patients with paired box gene 9 (*PAX9*) mutation. **Methods**·Patients with NSTA who visited the Department of Second Dental Center of Shanghai Ninth People′s Hospital, Shanghai Jiao Tong University School of Medicine, between January 2016 and December 2023 received whole-

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exome sequencing to screen *PAX9* mutation. The location and number of missing teeth were evaluated by oral pantomography, and dentofacial deformities were evaluated by X-ray cephalometrics. **Results**·Seven patients with *PAX9* mutation were included in the study, including 3 males (42.9%) and 4 females (57.1%). The patients were 7–31 years old at first visit, with a mean age of (19.7±8.0) years old. All the 7 patients were *PAX9* heterozygotes, of which 4 were missense and 3 were frameshift. The average number of missing teeth was 15.9±2.9. The number of missing teeth in maxilla (9.6±2.6) was slightly higher than that in mandible (6.3±2.4) (P=0.030). Maxillary second molar (100.0%), maxillary canine (85.7%) and mandibular second premolar (85.7%) were the three most common missing teeth, while mandibular lateral incisor (14.3%) and mandibular canine (14.3%) were the two least missing teeth. Patients with frameshift mutation had more missing teeth (18.3±2.1) than those with missense mutation (14.0±1.8) (P=0.032). X-ray cephalometrics analysis results showed that the angle sella-nasion-subspinale (SNA), angle nasion-subspinale-subspinale-porion (NA-Apo) and sella-nasion (S-N) in adult patients with *PAX9* mutation were significantly lower than the normal reference values, suggesting a shorter anterior cranial base and maxillary length. The frankfort horizontal plane-nasion-porion (FH-NPo) was higher than the reference value, and the Y-axis was lower than the reference value, indicating a more prognathic mandible. The angle subspinale-nasion-supramental (ANB) was lower than the reference value, indicating a skeletal angle Ⅲ malocclusion. The angle upper central incisor-nasion-subspinale (angle U1-NA) was higher than the reference value, indicating a lip inclination of maxillary central incisor. The angle lower central incisor-mandibular plane (IMPA) and lower central incisor-nasion-supramental (L1-NB) were lower than the reference values, indicating a retroclination of the mandibular central incisor, and crossbite in the maxillary and mandibular anterior teeth. **Conclusion**·The dentofacial phenotype of *PAX9*-mutated patients with NSTA is reported comprehensively. It is helpful to improve the understanding of the role of *PAX9* in human maxillofacial development.

[Key words] paired box gene 9 (*PAX9*); dentofacial deformities; X-ray cephalometrics; non-syndromic tooth agenesis; skeletal angle Ⅲ malocclusion

先天缺牙是最常见的发育异常，患病率为2.5%~13.4%[1-2]。其由遗传和/或环境因素决定。按照除智齿外的恒牙缺失数，先天缺牙可以分为：缺牙数<6颗的个别牙缺失、6颗≤缺牙数≤27颗的多数牙缺失和28颗恒牙全部缺失的先天无牙症。其中个别牙缺失相对常见，先天性多数牙缺失的患病率仅为0.084%~0.25%[3-4]，而先天无牙症则更为罕见。按照是否伴随其他症状（例如毛发、汗腺、指甲等其他外胚层衍生物发育异常），先天缺牙可分为非综合征型和综合征型2类。非综合征型先天缺牙（non-syndromic tooth agenesis，NSTA），又称为选择性牙齿发育不全（selective tooth agenesis，STHAG）。目前，超过80种基因已被明确会导致先天缺牙[5-6]。某些单基因突变［如组蛋白甲基转移酶2D（histone-lysine *N*-methyltransferase 2D，*KMT2D*）等］会同时影响面型和牙列，这充分表明同一基因可同时参与颌骨和牙齿的发育[7-12]。

配对盒基因9（paired box gene 9，*PAX9*）（OMIM*167416）突变是NSTA的最常见病因[6,13]。*PAX9*是配对盒转录因子家族的成员，位于14号染色体（14q13.3），由5个外显子组成，编码341个氨基酸。PAX9蛋白包含高度保守的配对DNA结合结构域（paired DNA binding domain，PD）和八肽基序（octapeptide motif，OM），其中PD包括N-末端亚结构域（N-terminal subdomain，NSD）、连接肽（linking peptide，LP）、C-末端亚结构域（C-terminal subdomain，CSD）[14-15]。PAX9在口腔间充质中高表达，是牙齿发育过程中骨形态发生蛋白4（bone morphogenetic protein 4，BMP4）、肌节同源盒蛋白1（muscle segment homeobox 1，MSX1）和淋巴增强子结合蛋白1（lymphoid enhancer-binding factor 1，LEF1）表达所必需的[4,16-22]。它还参与内侧鼻突、腭部和上颌骨的形成[23-24]。小鼠*Pax9*功能丧失导致牙齿缺失、腭裂和骨骼异常[24-25]。但目前为止，我们未检索到关于*PAX9*突变患者牙颌面表型的报道。本研究旨在通过X射线头影测量分析7名*PAX9*突变的NSTA患者的头颅定位侧位片，探究*PAX9*突变对人类颌骨发育的影响。

1 对象与方法

1.1 研究对象

本回顾性病例系列收集了2016年1月—2023年12月于上海交通大学医学院附属第九人民医院口腔第二门诊部就诊的7名*PAX9*突变的NSTA患者。纳入标准：①先天性恒牙缺失，否认因外伤、牙周病、牙体疾病导致牙齿后天缺失。②经曲面体层摄影片确认恒牙胚缺失。③经知情同意进行全外显子组测序，并确定为*PAX9*突变导致的NSTA。排除标准：①既往有正畸或正颌治疗史。②全身系统性疾病。③综合征型先天缺牙。④既往面部创伤。⑤根据全外显子组测序结果除*PAX9*之外还存在其他NSTA致病基因（如*MSX1*、*WNT10A*、*LRP6*等）。

1.2　研究方法

1.2.1　一般临床资料收集　从上海交通大学医学院附属第九人民医院电子病历信息系统获取患者的一般临床资料，包括性别、首诊年龄、全身重要临床体征（如皮肤、毛发、指甲、汗腺等外胚层来源组织异常情况等）。

1.2.2　影像学资料收集　患者初诊时拍摄曲面体层摄影片及侧位X射线头影测量片。根据曲面体层摄影片确定恒牙胚缺失及缺牙位置和数目，使用iOrtho11.0在线软件进行X射线头影测量分析。X射线头影测量参数包括：上牙槽座角（angle sella-nasion-subspinale，SNA）、颌凸角（angle nasion-subspinale-subspinale-porion，NA-APo）、前颅底长度（sella-nasion，S-N）、面角（frankfort horizontal plane-nasion-porion，FH-NPo）、Y轴角（Y axis）、上/下牙槽座角（angle subspinale-nasion-supramental，ANB）、上中切牙倾斜度（upper central incisor-sella-nasion，U1-SN）、上中切牙角（angle upper central incisor-nasion-subspinale，angle U1-NA）、上中切牙距（distance of upper central incisor-nasion-subspinale，distance U1-NA）、下中切牙-下颌平面角（angle lower central incisor-mandibular plane，IMPA）、下中切牙凸度（lower central incisor-nasion-supramental，L1-NB）。

1.2.3　遗传学资料收集　在患者及家系成员理解并签署知情同意书后，收集其外周静脉血样。使用基因组DNA提取试剂盒［天根生化科技（北京）有限公司］，根据说明书从患者及其家庭成员外周血样本中提取基因组DNA。使用Illumina平台进行全外显子组测序，平均深度为100×。对获得的突变进行过滤：①去除数据库1000 genomic data（1000 g_all）、esp6500siv2_all、gnomAD_ALL和gnomAD_EAS中任何一个数据库中最小等位基因频率>1%的突变。②保留外显子和剪接区（和外显子相邻的10 bp内含子区域）的保守突变。③删除经软件预测不会改变氨基酸序列的同义突变，并删除重复区中<10 bp的小片段非移码突变。④根据SIFT、Polyphen-2、MutationTaster软件的预测得分，保留至少2个软件支持其具有危害性的保守突变。

对先证者及其直系亲属采用Sanger测序，验证全外显子组测序结果。对先证者及直系亲属测序结果进行家系分离分析，证实全外显子组测序发现的候选致病性突变。

1.3　统计学分析

统计分析使用IBM SPSS Statistics 25.0软件和Graphpad prism 8软件完成。定性资料（如性别、突变类型等）采用构成比描述。对于定量资料（如首诊年龄、缺牙数目及头影测量参数），服从正态分布者采用$\bar{x}\pm s$描述，不服从正态分布者采用中位数和上/下四分位数描述其集中及离散趋势。对于正态分布方差齐性样本，采用独立样本t检验比较亚组间差异；非正态分布样本采用Mann-Whitney U非参数检验。以双侧P<0.05表示差异有统计学意义。

2　结果

2.1　一般情况

7例*PAX9*突变患者中男性3例（42.9%），女性4例（57.1%）。首诊年龄7~31岁，平均（19.7±8.0）岁（表1）。经病史采集、临床检查及影像学检查，7例患者除牙齿缺失外均未发现腭裂、骨质疏松以及其他外胚层衍生物异常，均诊断为NSTA。

表1　*PAX9*突变NSTA患者的一般信息和突变总结

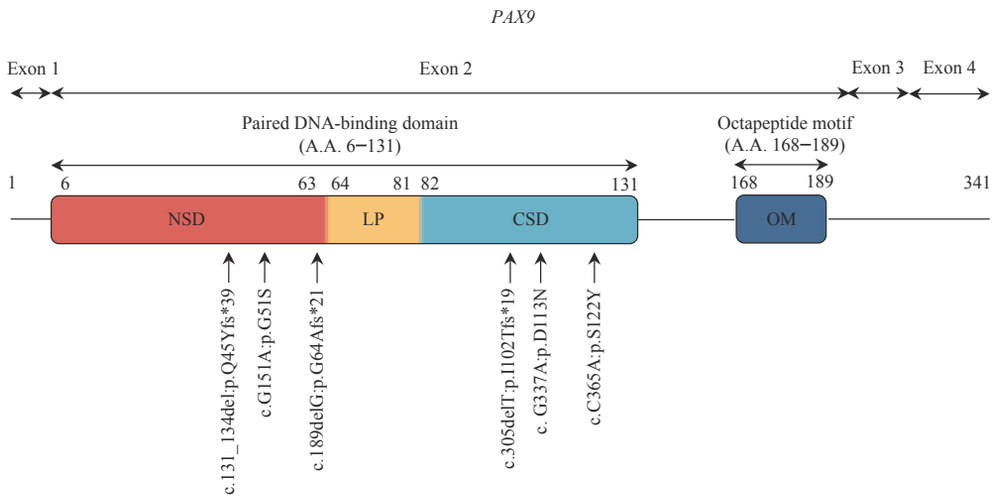
Tab 1　General information and summary of NSTA patients with *PAX9* mutation

Patient	Gender	Age/year	Nucleotide change	Amino acid change	Exon	Sub-domain	Zygosity	Type of mutation
1	Male	19	c.305delT	p.I102Tfs*19	2	CSD	Het	Frameshift
2	Female	13	c.C365A	p.S122Y	2	CSD	Het	Missense
3	Female	31	c.G151A	p.G51S	2	NSD	Het	Missense
4	Male	26	c.189delG	p.G64Afs*21	2	NSD	Het	Frameshift
5	Female	23	c.G151A	p.G51S	2	NSD	Het	Missense
6	Female	19	c.131_134del	p.Q45Yfs*39	2	NSD	Het	Frameshift
7	Male	7	c.G337A	p.D113N	2	CSD	Het	Missense

Note: NSD—N-terminal subdomain; CSD—C-terminal subdomain; Het—heterozygote.

2.2 突变情况

根据全外显子组测序结果，7例患者均携带*PAX9*杂合突变，其中4例为错义突变，3例为移码突变。突变位点均位于*PAX9*基因2号外显子高度保守的PD结构域内。病例3和病例5为无血缘关系的2名先证者，携带相同的突变位点（c.G151A：p.G51S）。4例患者的突变位于*PAX9*基因的NSD，3例患者突变位于*PAX9*基因的CSD。结果见表1、图1。



Note：A.A.—amino acid. N-terminus, 1–5; paired DNA-binding domain (PD), 6–131; N-terminal subdomain (NSD), 6–63; linking peptide (LP), 64–81; C-terminal subdomain (CSD), 82–131; octapeptide motif (OM), 168–189.

图1 *PAX9*突变NSTA患者的突变位点分布示意图

Fig 1 Distribution of variants in NSTA patients with *PAX9* mutation

2.3 缺牙情况

患者平均缺失恒牙（15.9±2.9）颗，上颌缺失数［（9.6±2.6）颗］多于下颌［（6.3±2.4）颗］（*P*=0.030），71.4%的位点左右侧牙缺失频率相同。乳牙滞留中位数4.0颗（上/下四分位数4.0/0）。从突变类型上来看，移码突变的患者缺牙数［（18.3±2.1）颗］多于错义突变的患者［（14.0±1.8）颗］（*P*=0.032）。从突变位置来看，突变位于NSD的患者缺牙数［（16.5±1.7）颗］与位于CSD的患者缺牙数［（15.0±4.4）颗］差异无统计学意义（*P*=0.550）。上颌第二磨牙（100.0%）、上颌尖牙（85.7%）、下颌第二前磨牙（85.7%）为最常见的缺失位点，下颌侧切牙（14.3%）、下颌尖牙（14.3%）为最少缺失的位点。值得注意的是，除了上颌第二磨牙之外，上下颌第一磨牙以及下颌第二磨牙也都有较高的缺失率。结果见图2。

Location	Right							Left						
	Mo2	Mo1	PM2	PM1	Ca	LI	CI	CI	LI	Ca	PM1	PM2	Mo1	Mo2
Max	100.0%	57.1%	57.1%	71.4%	85.7%	71.4%	42.9%	42.9%	71.4%	85.7%	57.1%	57.1%	57.1%	100.0%
Mand	57.1%	28.6%	85.7%	42.9%	14.3%	14.3%	42.9%	57.1%	14.3%	14.3%	42.9%	85.7%	57.1%	71.4%

Note：The prevalence of missing teeth is presented as a heat map. The darker the red, the higher the frequency of missing; the darker the blue, the lower the frequency of missing. White background represent missing frequency close to the average missing frequency of all sites in the dentition (56.6%). Max—maxilla; Mand—mandible; Mo2—the second molar; Mo1—the first molar; PM2—the second premolar; PM1—the first premolar; Ca—canine; LI—lateral incisor; CI—central incisor.

图2 *PAX9*突变NSTA患者的缺牙模式

Fig 2 Pattern of missing teeth in *PAX9*-mutated NSTA patients

2.4 牙颌面畸形

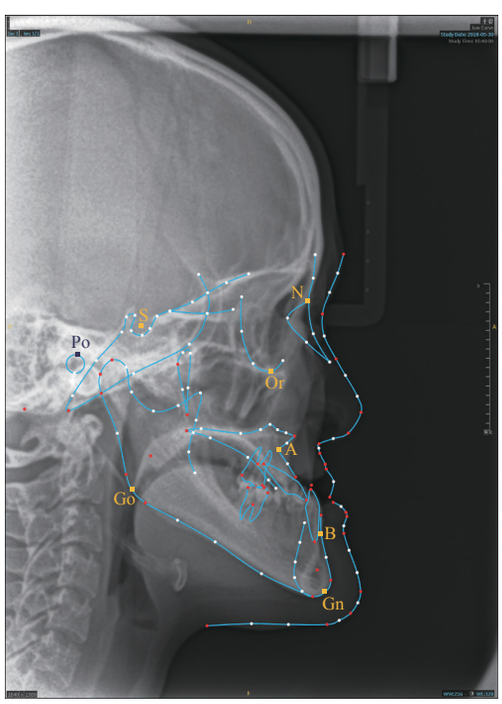
因病例2（13岁）和病例7（7岁）未进入下颌骨发育高峰期，故将其X射线头影测量结果单独列出。5例成年*PAX9*突变患者的X射线头影测量分析结果显示：SNA、NA-APo和S-N均明显小于正常参考范围，提示上颌后缩明显，前颅底矢状向发育不足；FH-NPo大于参考值、Y轴角小于参考值，提示下颌前伸；ANB小于参考值，提示骨性Ⅲ类错𬌗畸形；angle U1-NA大于参考值，提示上中切牙唇倾；IMPA、L1-NB小于参考值，提示下中切牙舌倾，上下前牙反𬌗倾向。除SNA处于正常范围内之外，2例未成年患者的X线头影测量结果与成年患者基本一致。结果见表2、图3。

表2　*PAX9*突变患者的X射线头影测量参数与经典正常值对比

Tab 2　Comparison between X-ray cephalometrics analysis parameters of patients with *PAX9* mutation and classical norms

Parameter	Adult *PAX9*-mutated patients	Underage *PAX9*-mutated patients		Classical norm
		Patient 2	Patient 7	
SNA/(°)	75.3±4.1	80.5	79.3	82.8±4.1
NA-APo(convexity)/(°)	−17.8±11.0	−25.0	−5.8	6.0±4.4
S-N/mm	62.3±2.4	62.5	60.9	71.0±3.0
FH-NPo/(°)	95.8±3.5	99.9	92.2	85.4±3.7
Y axis/(°)	53.6±2.9	48.7	55.4	64.0±2.3
ANB/(°)	−6.8±4.7	−9.8	−3.4	2.7±2.0
U1-SN/(°)	111.4±14.7	110.9	109.4	105.7±6.3
Angle U1-NA/(°)	36.1±16.9	30.4	30.1	22.8±5.2
Distance U1-NA/mm	6.6±5.1	5.8	3.7	5.1±2.4
IMPA(L1-MP)/(°)	76.6±13.1	76.2	76.0	96.7±6.4
L1-NB/mm	0.3±2.9	0.7	0.7	6.7±2.1

Note: Parameters below the classical norms are shown in green, parameters above the classical norms are shown in red, and parameters within the classical norms are shown in black.



Note：S—sella; N—nasion; Or—orbitale; A—subspinale; B—supramental; Gn—gnathion; Go—gonion; Po—porion.

图3　1例典型成年*PAX9*突变患者的侧位X射线头影测量片和头影测量标志点

Fig 3　Lateral X-ray cephalometric projection and cephalometic landmarks of a typical *PAX9*-mutated patient

3　讨论

本研究首次全面报道了*PAX9*突变NSTA患者的牙颌面特征。*PAX9*对多种器官和骨骼系统的发育至关重要。到目前为止，仅在小鼠中发现*Pax9*缺乏致死的证据，还没有关于人*PAX9*突变致死的病例报道。纯合*Pax9*突变小鼠出生后不久即死亡，表现出严重的腭裂，以及胸腺、甲状旁腺、牙齿和颅面骨骼发育缺陷[25]。在神经嵴来源的细胞中条件性敲除*Pax9*导致小鼠继发性腭裂和牙齿缺失，表明*Pax9*在神经嵴来源的组织中发挥重要作用[26]。

在基因组学上，本研究观察到的7例患者的*PAX9*突变全部位于2号外显子高度保守的PD内，表明PD是*PAX9*的突变热点位置。PD是一个高度保守的结构域，对PAX9蛋白和DNA结合至关重要[27]。PD突变影响PAX9蛋白的DNA结合活性、蛋白质稳定以及对牙齿发育至关重要的*MSX1*和*BMP4*基因的激活[6,28-29]。在突变类型上，与错义突变相比，移码突变导致的缺牙数更多。这些发现与先前关于*PAX9*突变患者的报道一致[13,28-35]。

就缺牙模式而言，*PAX9*突变患者上颌的缺失牙齿数量大于下颌，且磨牙缺失率高，而左右侧的缺失牙齿数量相当。目前已有研究尝试揭示*PAX9*影响磨牙发育的机制[36]。

在牙颌面表型上，*PAX9*突变患者呈现上颌后缩、下颌前伸的骨性Ⅲ类错𬌗畸形，上下前牙呈相反趋势。NSTA和骨骼模式之间存在的关系可能有以下几个原因：①神经嵴是牙本质、牙骨质以及颌骨的共同来源，因此，可以假设NSTA患者的骨骼模式可能是独特的。②根据MOSS等[37]的功能基质理论，骨骼的生长是对其功能单元建立的功能关系的反映；牙齿作为颌骨生长过程中的一个功能单元，牙胚缺失会导致相应的颌骨发育不全。③长期缺牙导致的颌骨功能代偿。

1974年，WISTH等[38]发现，在先天缺失1~6颗恒牙的9岁儿童中，上颌后缩，且即使先天缺失的牙齿仅位于下颌，ANB也显著减少，上颌基部更短，上切牙的倾斜度增加。ROALD等[39]对NSTA患者

进行了7年的追踪随访，研究了其面型侧貌的变化，发现在生长发育过程中始终呈现上颌缩短的特征，并认为9~16岁NSTA患者的颅面结构变化与没有缺失恒牙的一般人群大致相同，提出NSTA对一般生长模式的影响很小，对这类患者进行正畸治疗应遵循与非先天缺牙儿童相同的治疗指南。SARNÄS等[40]记录了141例NSTA患儿（男59例，女82例）从8~18岁的面部轮廓的生长变化，在大约2/3的患儿中发现了轻微的生长变化，尤其是与下颌骨的位置和形状有关的头影测量参数。OGAARD等[41]发现随着先天缺失牙齿数量的增加，NSTA患者下颌平面角和前下面部高度减小，其余骨骼参数与一般人群相比几乎没有差异；其结论是，NSTA患者典型的牙面结构可能是由于牙齿和颌骨功能代偿形成的，而不是不同的生长模式所致。

与此同时，BEN-BASSAT等[42]的研究报道了与上述相似的特征，但研究者认为这些特征可能是由于缺少牙胚而导致根尖基部颌骨发育不全造成的。ENDO等[43]研究了8.5~19岁的日本NSTA患者，发现患者的颅底长度和角度较小，上颌长度较短；上牙槽座点和SNA显著后退。因此认为，NSTA患者的上颌骨后缩是由上颌骨前部生长不足引起的。BJÖRK[44]用微种植体的方法研究了一般人群上面部的骨缝生长，发现上颌结节是上颌骨的主要生长中心，上颌骨的长度生长几乎全部来源于上颌结节区；除了牙槽突外，在上颌骨的前表面没有发现骨膜附着导致的长度增长。本研究同样观察到前颅底变短和上牙槽座点的后退，因此推测*PAX9*突变患者特征性的磨牙缺失可能通过影响上颌骨后部（包括上颌结节）的骨生成导致上颌生长不足。

总之，大多数研究发现，NSTA患者的上颌骨较短，下颌前伸，下颌平面角较小，上颌和下颌切牙后倾较大，且这些特征的严重程度受到牙齿缺失数量的影响。而导致这一表型的原因仍无定论，需要更多的研究进行探索。

*PAX9*突变导致的骨性Ⅲ类错𬌗畸形是这类患者口腔修复临床治疗中的难点，无论是种植义齿固定修复还是活动修复，都面临着咬合关系不佳的困难。因此NSTA患者有必要接受早期基因诊断，并在生长发育阶段给予早期矫治等干预措施，以防止或减轻成年后严重的骨性Ⅲ类错𬌗。

由于先天性多数牙缺失极低的发病率，且*PAX9*仅作为其遗传原因的一部分，故其发病基数更低。因此本文受限于*PAX9*突变患者有限的样本量，未根据年龄、性别进行分组分析。未来的研究有待基于更大的样本量，对不同致病基因引起的NSTA患者进行对比分析，以建立与缺牙模式类似的牙颌面表型模式。

综上所述，本研究报道了*PAX9*突变NSTA患者的牙颌面畸形情况，并报道了其缺牙模式，有利于增进对*PAX9*在人类颌面部生长发育中作用的认识。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclose no relevant conflict of interests.

伦理批准和知情同意/Ethics Approval and Patient Consent

本研究涉及的所有实验均已通过上海交通大学医学院附属第九人民医院伦理委员会的审核批准（审批号：SH9H-2023-T366-1）。所有实验均遵照2013年修订的《赫尔辛基宣言》的条例进行。受试对象或其亲属已经签署知情同意书。

All experiment protocols in this study were reviewed and approved by Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (Approval Letter No. SH9H-2023-T366-1), and all experiments were carried out by following the guidelines of *Declaration of Helsinki* as amended in 2013. Consent letters have been signed by the research participants or their relatives.

作者贡献/Authors' Contributions

窦嘉琪负责研究方案制定、数据收集分析和论文撰写及修改；高洁和卞晓玲负责临床病例收集；王凤负责论文修改；代庆刚参与研究方案制定、课题指导和论文修改；吴轶群负责研究方案制定、课题指导和论文修改。所有作者均阅读并同意了最终稿件的提交。

DOU Jiaqi was responsible for conceptualization, investigation, data curation, writing original draft, review and editing; GAO Jie and BIAN Xiaoling participated in clinical case collection; WANG Feng was responsible for review and editing; DAI Qinggang participated in conceptualization, supervision, review and editing; WU Yiqun was responsible for conceptualization, supervision, review and editing. All the authors have read the last version of paper and consented for submission.

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