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Review Article

A review on non-syndromic tooth agenesis associated with *PAX9* mutations

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Summary Tooth agenesis in the reduction of tooth number which includes hypodontia, oligodontia and anodontia is caused by disturbances and gene mutations that occur during odontogenesis. To date, several genetic mutations that unlock the causes of non-syndromic tooth agenesis are being discovered; these have been associated with certain illnesses because tooth development involves the interaction of several genes for tooth epithelium and mesenchyme odontogenesis. Mutation of candidate genes *PAX9* and *MSX1* have been identified as the main causes of hypodontia and oligodontia; meanwhile, *AXIN2* mutation is associated with anodontia. Previous study using animal models reported that *PAX9*-deficient knockout mice exhibit missing molars due to an arrest of tooth development at the bud stage. *PAX9* frameshift, missense and nonsense mutations are reported to be responsible; however, the most severe condition showed by the phenotype is caused by haploinsufficiency. This suggests that *PAX9* is dosage-sensitive. Understanding the mechanism of genetic mutations will benefit clinicians and human geneticists in future alternative treatment investigations.

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Contents

1. Introduction

Tooth agenesis involving reduction of tooth number also known as congenitally missing teeth, is due to a craniofacial malformation. The teeth are fail to erupt in the oral cavity and mineralization is not visible in radiographs [1,2]. It can be subdivided into three types which are hypodontia, oligodontia and anodontia, as summarized in Table 1.

A person is diagnosed with hypodontia when there is an absence of one to six teeth excluding the third molar, while oligodontia refers to the absence of more than six teeth excluding the third molar. However, the most severe condition is anodontia, which refers to the absence of all teeth [3,4]. Anodontia is normally present alongside syndromic conditions such as Witkop tooth—nail syndrome, Fried syndrome, Böök syndrome (PHC), hair—nail—skin—teeth dysplasias, Rieger syndrome, Holoprosencephaly, Down's syndrome (trisomi 21), Wolf—Hirschhorn syndrome (deletion 4p) and Kabuki syndrome [5—8]. Meanwhile, other types of tooth agenesis conditions may appear as syndromic or non-syndromic [3,8,9].

Since oral health plays a significant role in one's life, tooth agenesis may cause the affected person to have improper masticatory function, suffer from speech alteration and develop aesthetic problems especially where teeth at the anterior region are missing. Tooth agenesis also causes some other problems, including affecting a person's emotions [9—11].

To date, the mechanism of tooth development is well understood, with the aetiology of tooth agenesis being linked to both environmental and genetic factors [2,8,12]. This paper discusses the mutation gene candidate *PAX9* that is responsible for early tooth development and the assertion that its mutations are associated with several types of tooth agenesis.

2. Prevalence, distribution and pattern of tooth agenesis

Severe tooth agenesis (absence of 4 or more teeth excluding the third molars) has an estimated prevalence of 0.25% in the general population [4]. However, hypodontia is identified as the most common dental anomaly in humans and affects almost 20% of the current population [10,13]. As reported by Nik Hussein, hypodontia is the most common tooth anomaly in Malaysia with a prevalence of 2.8%; meanwhile the updated prevalence (including the third molar) is 3.2% [14,15], however there are no published reports on the prevalence of oligodontia and anodontia in Malaysia.

Several studies have found that females are more affected with tooth agenesis compared to males. The highest prevalence (7.7% in female and 6.1% in male) was found in Chinese population, while one meta-analysis reported a female to male ratio of 1:1.4 [14,16,17]. The pattern of tooth agenesis varies by population. Previous studies conducted among Caucasians report that the lower second premolars and upper lateral incisors are the most common missing teeth after third molars, whilst American blacks have a lower prevalence of congenitally missing teeth than American whites [18,19]. In Asians, the most common missing teeth after the third molar are second premolars and mandibular lateral incisors; however, in Malaysia, upper lateral incisors (1.7%) followed by lower and upper second premolars (1.5%) were identified as the most common missing teeth [11,14].

Table 1 Summary on type of tooth agenesis and its associated criteria.

Tooth agenesis	Number of missing tooth	Level of severity	Classification	Type of inheritance
Hypodontia	1—6 teeth (excluding third molar)	Mild to moderate	Syndromic and non-syndromic	Sporadic or familial
Oligodontia	More than 6 teeth	Severe	Syndromic and non-syndromic	Sporadic or familial
Anodontia	Complete absence of teeth	Severe	Syndromic	Sporadic or familial

Table 2 List of odontogenesis components and genes at each development stage.

Stages	Components/genes				
Bud stage	*MSX1* *PAX9*	*FGF* *Shh*	*Glil* *BMP4*	*Ptc* *EGF*	*LEF1*
Cap stage	*AXIN2* *MSX1*	*Pitx2* *Shh*	*BMP2* *EDA*	*TGF*	
Bell stage	*PAX9* *MSX1*	*TGF* *BMP4*	*BMP2* *AXIN2*		

3. Embryonic tooth development

Tooth development results from several interactions which act synergistically and antagonistically, leading to tooth epithelium and mesenchyme formation during embryonic odontogenesis. The process is governed by several components and mechanisms involving expression of several transcription factors, Sonic hedgehog (*Shh*), Wingless (*Wnt*) signaling families, fibroblast growth factors (*FGF*s), bone morphogenic proteins (*BMP*) and also cellular matrix molecules [9,20—24]. This complex mechanism consisting of the continuous and progressive stages of odontogenesis have been divided into bud, cap and bell stages [25,26].

During embryonic tooth development, dental lamina is resulted from thickening of the oral epithelium and invagination into the surrounding ectomesenchymal cells, forming the tooth bud. The epithelium proliferates and condenses to form the dental papilla and dental sac. Later, the bud further proliferates to form a cap-shaped enamel organ that surrounds the mesenchymal papilla. Continued growth and differentiation of adjacent epithelium and mesenchymal cells lead to formation of ameloblast and odontoblast cells which later develop into the enamel and dentin respectively [21,22,25].

In 2008, more than 300 genes were listed in the database created by Pekka Nieminen from Helsinki University, Finland (http://bite-it.helsinki.fi) containing compilations of expression patterns at various stages of odontogenesis [27,28]. Several genes, transcription factors, growth factors and extracellular matrix molecules involved in odontogenesis are listed in Table 2 [20,22,29].

4. Genetic basis of tooth agenesis

Advancement in genetics and molecular biology technology has allowed us to better understand the aetiology of tooth agenesis. Tooth morphogenesis is monitored under strict genetic control during embryonic development and these genes are being discovered at an increasing rate. Any disturbances and gene mutations that occur during odontogenesis are believed to cause missing teeth and also dental defects such as changes in tooth size, morphology, and cytodifferentiation [28,30,31].

Mutation of genes *PAX9* (further discussed in the next part) and *MSX1* have been identified as the main causes of hypodontia and oligodontia; meanwhile, *AXIN2* mutation is associated with anodontia [2,32—34]. *PAX9* and *MSX1* are members of paired-box and homeobox transcription factors respectively, which are involved in the early stages of tooth development. Mutation of *MSX1* is associated with missing premolars and certain syndromic conditions such as cleft lip/palate and Witkop syndrome [35,36]. The *MSX1* gene located at chromosome 4 is important for determination of the shape and position of teeth [37].

AXIN2 located at chromosome 7 is the gene responsible for encoding axis inhibition protein 2 that regulates the stability of beta-catenin. This gene is associated with familial oligodontia and anodontia; additionally, the affected person has a higher susceptibility to colorectal cancer [38—40]. *AXIN2* acts as a regulator in the *Wnt* signaling pathway and its expression is found in the enamel knot [20]. However, this paper will focus on mutations that occur within the *PAX9* gene which has been reported by several studies (Table 3).

5. *PAX9* (paired box gene 9) mutations experimental evidences

PAX9 is a member of the paired box transcription factor protein which contains an octapeptide, a pair of box domains and a 128-amino acid long paired-type homeodomain that plays a critical role in dental mesenchyme formation at all stages of odontogenesis [41]. This gene is found on chromosome 14 at cytogenetic location 14q13.3 (Fig. 1) and is strongly expressed in the oral mesenchyme during the early stages of tooth development [9,22].

PAX9 is responsible for *BMP4* expression which further regulates expression of *MSX1*. Thus, mutations of *PAX9* cause abnormal or reduced downstream protein regulation function which is important for tooth development [20,21]. Animal model studies have proven that *PAX9*-deficient knockout mice exhibit missing molars due to an arrest of tooth development at the bud stage [42].

PAX9 mutations occur from the range of single nucleotide substitutions: by changing one amino acid, premature termination and abolished protein function to haploinsufficiency. This suggests that *PAX9* is dosage-sensitive whereby greater mutations showing more severe tooth agenesis phenotypes [42,43]. Mutations in both coding and non-coding regions have been reported involving exons 1, 2, 3 and 4; exon 2 which is a highly conserved area containing paired-domain regions showed the most mutations [2]. All these mutations are associated with oligodontia and hypodontia, particularly causing missing molars. In most cases, the mutation is inherited as autosomal dominant with incomplete penetrance, though an autosomal recessive inheritance mode has also been reported in a Pakistani family [2,37].

5.1. Frameshift mutation

Changes in amino acid sequences affect protein function and expression. Several frameshift mutations have been reported occurring at exon 2 and exon 4 involving insertion and deletion mutations. Das et al. reported that deletion of 8 nucleotides followed by insertion of 288 foreign nucleotides (175_188, del_8ins_{288}) within exon 2 lead to disruption of the C-terminal DNA binding domain of *PAX9* paired-domain. The affected person was a twin with missing permanent molars [43]. Deletion of several nucleotides (619_621, del_3ins_{24}) fol-

Table 3 List of mutations occurring within the *PAX9* gene according to type of mutation.

Type of mutation	Classification	Nucleotide	Molecular consequence	Phenotype	References
Frameshift	Deletion > insertion	175_188 (del_8inse_{288})	Disruption of C-terminal binding region	Hypodontia	[43]
	Deletion > insertion	619_621 (del_3ins_{24})	Premature termination of protein translation	Oligodontia	[41]
	Insertion	218_219_{insG}	Extension of several G-series	Oligodontia	[44,45]
	Insertion	792_793_{insC}	Protein truncation and termination	Oligodontia	[46]
	Deletion	230_242_{del13}	Disruption of protein translation	Oligodontia	[38]
	Deletion	465_{delG}	Disruption of protein translation	Hypodontia	[47]
	Deletion	462_{delT}	Disruption of protein translation	Hypodontia	[47]
	Insertion	624_625_{insA}	Disruption of protein translation	Hypodonita	[47]
Nonsense	Deletion	14q locus	Abolished protein function (Haploinsufficiency)	Hypodontia	[48]
	Transition	1A > G	Abolished protein function (Haploinsufficiency)	Oligodontia	[49]
	Transition	2T > G	Abolished protein function (Haploinsufficiency)	Oligodontia	[50]
	Substitution	340A > T	PAX9 premature termination at N-terminal DNA binding region	Oligodontia	[51]
	Substitution	480C > G	Premature stop codon	Hypodontia	[45]
Missense	Substitution	62T > C	Reduction of DNA binding ability and specificity	Hypodontia	[43]
		271A > G		Hypodontia	[43]
		76C > T		Oligodontia	[53]
		83G > C		Oligodontia	[52]
<END>[5pt]		238A > G	Reduction of DNA binding ability and specificity	Oligodontia	[38]
		428A > G			
		152G > C			
<END>[5pt]		718G > C	Structural PAX9 protein sequence (polymorphism)	Hypodontia	[54]
Silent	Substitution	717C > T	No significant changes in sequences	Hypodontia	[54]

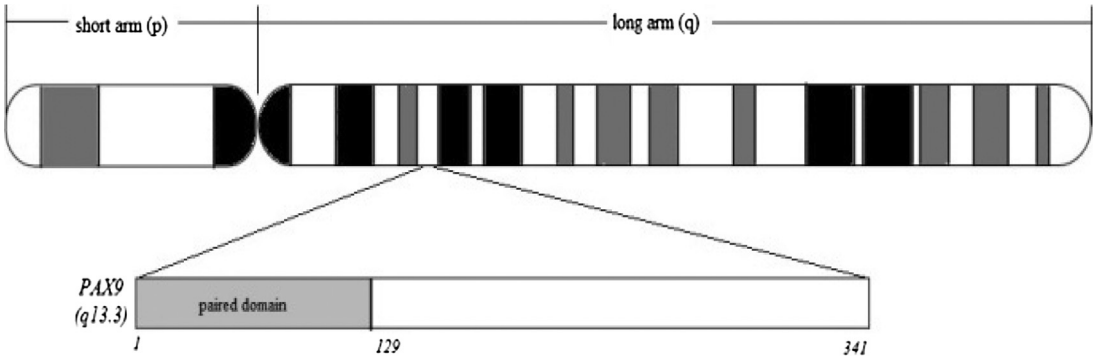

Figure 1 Location of *PAX9* gene within chromosome 14.

lowed by 24 bp foreign insertion and several duplications of 5′splicing site sequences occurring at the end of exon 2 caused premature termination of translation at aa 210. Aberrant splicing lead to frameshift mutation and premature termination of translation at aa 314. The proband had molar oligodontia [41].

Other than that, an oligodontia patient with missing molars, premolars and incisors showed insertion of a single guanine nucleotide (218_219_{insG}) within the exon 2 *PAX9* paired-domain region, causing a frameshift between N- and C-terminal DNA binding domains due to extension of several guanine series [44]. The same mutation was also found in a female Chinese oligodontia patient with 15 missing permanent teeth [45].

A single cytosine nucleotide insertion (792_793_{insC}) at the N-terminal DNA binding region caused *PAX9* protein truncation and lead to premature termination of translation at aa 315. This mutation occurred within exon 4 and the patient showed an autosomal dominant trait of missing molars and premolars [46].

Recently, Bergandal et al. reported that mutational analysis of an oligodontia patient with 13 missing teeth showed deletion of 13 nucleotides (230_242_{del13}) at the *PAX9* paired-domain upstream region [38].

Another two frameshift mutations within *PAX9* exon 3 reported in two female Malaysian hypodontia patients who are missing first molar and lateral incisor showed deletion of single nucleotide, c.465delG and c.462delT respectively [47]. The same study also reported another insertion mutation c.624_625insA as the affected person is also hypodontia female patient with missing a canine tooth [47].

5.2. Nonsense mutation

Nonsense mutations mostly cause changes in amino acids that code for stop codon. A study reported an infant hypodontia patient has normal anterior teeth but missing both maxillary and mandibular molars and premolars. *PAX9* gene in the patient showed deletion of the 14q locus. This mutation suggests haploinsufficiency, since only one copy of the *PAX9* gene was able to function normally [48].

Transition mutation M1V (1A > G) at the start codon of exon 1 caused haploinsufficiency where only one copy of the gene functioned normally, while the other was not expressed due to abolished protein function. The affected person was diagnosed with oligodontia, inherited as autosomal dominant as permanent incisors, premolars and molars were missing [49]. Another transition mutation was found recently at the start codon (2T > G) which resulted in an ATG initiation start codon instead of ACG. The mutation was detected in mutational analysis of a 12-year old Chinese oligodontia patient [50].

Premature termination of *PAX9* gene caused by substitution of Lys114stop (340A > T) occurring at the ${}_{A}340_{T}$ switch lead to truncation and termination of protein at the N-terminal end of DNA binding region [51].

Mutational analysis from a recent study conducted by Zhu et al. reported a sporadic Chinese infant hypodontia patient showing nucleotide substitution (480C > G) within exon 2, causing nonsense mutation. This mutation suggested haploinsufficiency due to a premature stop codon which reduced the transcriptional activity of *PAX9*. The affected person was congenitally missing 6 primary molars and 20 permanent teeth [45].

5.3. Missense mutation

Nucleotide substitution is the most reported missense mutation. Two studies show nucleotide substitution occurring within the DNA binding region of *PAX9* paired-domain which involves substitution of Leu21Pro (62T > C) and Lys91glu (271A > G), respectively. The affected person showed an oligodontia phenotype with missing molars, premolars and incisors [43].

Meanwhile, substitution mutation occurring at the N-terminal DNA binding region of the *PAX9* paired-domain was reported in two studies. Substitution of Arg26Tyr (76C > T) and Arg28Pro (83G > C) affect DNA binding specificity, thus lead to reduction in DNA binding ability. The phenotype of the affected person showed oligodontia with missing molars, premolars and incisors [52,53].

Polymorphism 718G > C leading to substitution of Ala240Pro and causing structural changes in *PAX9* protein sequences has been reported in Portugese families. The probands showed missing lateral incisors [54]. Recently, Bergendal et al. reported three substitution mutations in Swedish oligodontia patients which are Thr80Ala (238A > G), Tyr143Cys (428A > G) and Gly51Ala (152G > C) [38].

5.4. Silent mutation

One silent mutation occurring within exon 3 involving substitution (717C > T) has been reported. It was found in a Portugese hypodontia proband who was missing a lateral incisor. No significant changes were observed in the *PAX9* protein sequence but the phenotype of the proband was nevertheless affected [54].

6. Conclusion

Improper masticatory function and aesthetic problems caused by tooth agenesis may affect the patients' daily life. Because embryonic tooth development involves complex signaling cascades and the expression of several genes, disturbances that occur during the process may lead to tooth agenesis. At present, several candidate genes have been identified as genetic causative agents for tooth agenesis such as *MSX1* and *AXIN2*; however, the highest number of mutations was found in the *PAX9* gene. Experimental evidence shows how *PAX9* mutations ranging from single nucleotide substitutions to changes in amino acid and premature termination to haploinsufficiency. This suggests that the phenotype of the affected person is dosage-sensitive. A comprehensive understanding of the genetic mutations and mechanisms that cause tooth agenesis will benefit patients, clinicians and geneticists in providing alternative treatment plans in the future.

Conflict of interest

The authors declare that no conflicts of interest concerned in this study.

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