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MINI REVIEW

Prevalence and genetic basis of tooth agenesis

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Abstract Tooth agenesis or hypodontia is one of the most common anomalies of the human dentition, characterized by the developmental absence of one or more teeth. Many studies have reported that the prevalence of congenital absence of permanent teeth varies from 3% to 11% among European and Asian populations. Recent advances in the fields of molecular biology and human genetics have improved our understanding of the cause of tooth agenesis. In this review, we assess the previous literature on prevalence of tooth agenesis comparing the Japanese with other racial populations, and describe the recent genetic studies associated with hypodontia in human and mouse models.

1. Introduction

Tooth agenesis is the most clearly recognized developmental dental anomaly in humans and can be challenging to manage clinically. Hypodontia is often used as a collective term for congenital absence of primary or secondary teeth, although specifically it describes the absence of one to six teeth excluding third molars. Oligodontia refers to the absence of more than six teeth, excluding third molars, while anodontia represents the loss of all teeth [1,2]. There are large differences in the prevalence of dental agenesis among different racial populations [1,3—26]. Dental agenesis affects more frequently the permanent rather than the primary dentition [4,10]. The condition may appear as part of a recognized genetic syndrome or as a non-syndromic, familial form, which occurs as an isolated trait [2,27]. Both forms of congenital absence of tooth have been connected with mutations of related genes. The purpose of this review is to assess the previous literature on congenital absence of permanent teeth comparing the prevalence in Japan with that in other countries. Another purpose is to describe the recent human genetic studies on hypodontia and molecular genetic researches using mouse models with tooth agenesis.

2. Prevalence of dental agenesis of permanent teeth

Non-syndromic hypodontia is the most common form of congenital tooth absence, which involves variable numbers of teeth. Many studies on the prevalence of dental agenesis of permanent teeth have been published so far [1,3—26]. Third molars are the most commonly absent teeth in the dentition. When the third molar is excluded from studies, then the reported prevalence rates for each tooth vary according to the population. Large differences in the prevalence of dental agenesis have been reported, varying from 1.4% in Japanese [5] to 11.3% in the Irish population

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[21]. The wide range in dental agenesis prevalence rates could be ascribed to differences in the racial derivations of the groups examined, sampling methodologies, diagnostic criteria, age distribution and sample sizes [1,12,15,19]. Previous literature for this review was selected according to the following criteria: the sample consisted of more than 1000 persons; the diagnosis of dental agenesis was based on radiographic examination; the report presented prevalence of agenesis excluding the third molar; and the report did not mix the prevalence of agenesis of primary teeth. Table 1 summarizes the results from studies previously published on the prevalence of congenital absence of permanent teeth [1,3—26].

Focusing on the reports from outside of Japan, the prevalence of dental agenesis varied from 2.8% in the Turkish [16] to 11.3% in the Irish population [21]. In most reports, the prevalence of dental agenesis in females was always higher than in males; however Rølling [18] and Albashaireh and Khader [15] reported that there were no significant a difference based on sex. The prevalence of dental agenesis in females was 1.01 times [18] to 1.64 times [17] higher than in males. The types of teeth reported missing varied in different ethnic groups. In Europeans, the mandibular second premolar was most frequently absent, followed by the maxillary lateral incisor and second premolars [17—22]. In the Malaysian [14], Turkish [16] and American populations [26], the most frequently missing tooth was the maxillary lateral incisor; and, in Chinese, it was the mandibular central and lateral incisors [13]. The absence of maxillary central incisor, canine, first molar and second molar was rare. The prevalence of oligodontia, referring to the absence of more than six teeth, varied from 0% [13] to 0.43% [26] of the population. Unilateral occurrence of hypodontia is more common than bilateral occurrence. In case of missing of two or more teeth, however, symmetrical hypodontia is predominant [13,17,24].

Most of the Japanese reports on hypodontia were written in Japanese. We were able to find 11 reports [1,3—12] investigating the prevalence of congenital absence of teeth in the Japanese population. Of these, only three reports [1,6,12] were published in English. In the Japanese population, the prevalence of congenitally missing permanent teeth varied from 1.4% [5] to 9.9% [8]. We took an average of the prevalence of tooth agenesis reported by previous Japanese studies [1,3—12]. Tooth agenesis of permanent teeth was found in 2200 persons on examination of a total of 31,992 Japanese subjects. The prevalence of tooth agenesis was 7.6% in females and 6.0% in males (ratio 1.26:1), and for both sexes combined it was 6.9%. This prevalence is near the middle of the reported range. The mandibular second premolar was the most frequently absent in 31,992 Japanese accounting for 27% of the total missing teeth, excluding the results of two reports [4,7] because of lack of the detailed teeth number. The mandibular lateral incisor was the second frequently absent (17%) tooth followed by the maxillary second premolar (15%) and the maxillary lateral incisor (13%). Similar to the European population, the mandibular second premolars were most frequently missing (27%), however, the percentage of the total missing teeth was lower than that of other populations (29% [22] to 57% [25]). In addition, a significant number of missing mandibular lateral incisors was reported in Japanese. This finding was quite different from the previous studies in Caucasians, but similar to other Asian populations [13,14]. Absence of the maxillary central incisor and the first molar were extremely rare in hypodontia of Japanese subjects. On the other hand, the involvement of the canine and second molar was common in hypodontia of the Japanese compared with other populations [1,4,9,11,12]. A total of 4347 permanent teeth were absent in 2200 Japanese subjects with dental agenesis, at an average of 1.99 teeth per person. This number is much higher than that of other countries. The prevalence of oligodontia was 0.19%, excluding the results of two reports [11,12] which lacked data regarding the prevalence of oligodontia. Goya et al. [1] has reported the prevalence of hypodontia in Japanese pediatric patients and confirmed that hypodontia was not uncommon in Japanese populations compared with other racial populations. Endo et al. [12] has reported that the distinct characteristic of dental agenesis in Japanese compared with other populations was a higher prevalence of both oligodontia and mandibular lateral incisor agenesis.

3. Genetic basis of tooth agenesis

3.1. Non-syndromic tooth agenesis

Non-syndromic or familial hypodontia is more common than the syndromic type. This condition can follow autosomal dominant [28—30], autosomal recessive [31,32] or X-linked [33] patterns of inheritance, with considerable variation in both penetrance and expressivity. Recent advances in the fields of molecular biology and human genetics have improved our understanding of tooth development. Gene targeting experiments in mice have established the genetic associations with hypodontia. *Muscle segment homeobox 1* (*Msx1*) gene deficient mice manifested secondary cleft palate, deficiency of mandibular and maxillary alveolar bone and failure of tooth development [34]. *Msx1* thus had a critical role in mediating epithelial—mesenchymal interactions during craniofacial bone and tooth development. In humans, genetic linkage analysis of a family with autosomal-dominant selective hypodontia demonstrated a mutation in the *MSX1* gene [28,35—38] (Table 2). *MSX1* mutations predominantly affect second premolars and third molars, sometimes in combination with other types of teeth including the first molar. On the other hand, in more common cases of incisor-premolar type of hypodontia, genetic analysis has excluded *MSX1* gene as the causative locus for this type of hypodontia in five Finnish families [39] and in five Japanese families [40].

Gene knockout experiments in mice have revealed that *paired box 9* (*Pax9*) is essential for the development of a variety of organs and skeletal elements, and necessary for the dental mesenchyme to condense around the tooth bud epithelium [41]. Tooth development of *Pax9*-deficient mice is arrested in the bud stage, and *Pax9* is required for the mesenchymal expression of *Msx1*, *bone morphogenetic protein 4* (*Bmp4*) and *lymphoid enhancer binding factor 1* (*Lef1*) [41]. These suggest a role for *Pax9* in the establishment of the inductive capacity of the tooth mesenchyme. In human, mutations in *PAX9* are associated with unique phenotypes of familial tooth agenesis that mainly involve posterior teeth.

Table 1 Previous data on congenitally missing permanent teeth in various populations.

Nationality of subjects	Author	No. of subjects	Prevalence total (female:male)	Most/second most frequently missing teeth (%)[a]	No. of missing teeth per affected person	Prevalence of oligodontia
Japanese	Okamoto et al. [3]	1,001	5.6% (1.56:1)	12, 22 (32%)/32, 42 (20%)	1.65	0.10%
	Terasaki and Shiota [4]	1,871	8.7% (1:1)	35, 45/12, 22	1.60	0.27%
	Tsutsui and Yoshida [5]	1,454[b]	1.4% (1.95:1)	12, 22 (13%)/31, 41 (10%)	1.43	0%
	Niswander and Sujaku [6]	4,150	6.6% (1.59:1)	32, 42 (34%)/35, 45 (25%)	1.57	0.07%
	Nakahara et al. [7]	3,435	8.6% (1.04:1)		1.62	0.12%
	Ishizuka et al. [8]	1,000[b]	9.9% (1.08:1)	35, 45 (28%)/15, 25 (17%)	1.87	0%
	Yanagida and Mori [9]	4,009[b]	7.8% (1.04:1)	35, 45 (26%)/32, 42 (24%)	1.86	0.05%
	Ogita et al. [10]	6,299[b]	2.8% (1.10:1)	35, 45 (33%)/15, 25 (21%)	1.87	0.10%
	Hirukawa et al. [11]	3,343[b]	9.4% (1.08:1)	35, 45 (25%)/15, 25 (17%)	2.27	
	Endo et al. [12]	3,358[b]	8.5% (1.24:1)	35, 45 (27%)/15, 25 (16%)	2.4	
	Goya et al. [1]	2,072[b]	9.4% (1.24:1)	35, 45 (30%)/15, 25 (17%)	2.84	1.35%
Total		31,992	6.9% (1.26:1)	35, 45 (27%)/32, 42 (17%)	1.99	0.19%
Chinese	Davis [13]	1,093	6.9% (1.27:1)	31, 41, 32, 42 (60%)	1.5	0%
Malaysian	Nik-Hussein [14]	1,583[b]	2.8% (1.63:1)	12, 22 (31%),/32, 42 (22%)	1.8	0.19%
Jordnian	Albashaireh and Khader [15]	1,005[b]	5.5% (1.12:1)	35, 45 (37%)/12, 22 (30%)	1.69	
Turkish	Altug-Atac and Erdem [16]	3,043[b]	2.8% (1.29:1)	12, 22		0.13%
Swedish	Bergström [17]	2,589	7.4% (1.64:1)	35, 45 (41%)/12, 22 (23%)	1.81	0.19%
Danish	Rølling [18]	3,325	7.8% (1.01:1)	35, 45 (30%)/15, 25 (16%)	1.77	0.15%
Norwegian	Aasheim and Ogaard [19]	1,953	6.5% (1.23:1)	35, 45 (50%)/15, 25 (20%)	1.71	0.10%
Norwegian	Nordgarden et al. [20]	9,532[b]	4.5% (1.28:1)	35, 45 (46%)/15, 25 (20%)	1.8	0.09%
Irish	O'Dowling and McNamara [21]	3,056[b]	11.3% (1.2:1)	35, 45 (37%)/12, 22 (19%)	1.95	0.43%
British	Rose [22]	6,000[b]	4.3% (1.43:1)	35, 45 (41%)/12, 22 (24%)	1.86	0.17%
Icelandic	Magnússon [23]	1,116	7.9% (1.33:1)	35, 45 (53%)/15, 25 (19%)	1.90	0.18%
Canadian	Thompson and Popovich [24]	1,191	7.4% (1.48:1)	35, 45 (35%)/12, 22 (23%)	1.61	0.08%
U.S.A	Byrd [25]	2,835	2.8% (1.36:1)	35, 45 (57%)/12, 22 (17%)	1.84	
U.S.A	Muller et al. [26]	13,459[c]	3.5% (1.42:1)	12, 22 (38%)/35, 45 (30%)	1.81	0.05%
		1,481[d]	3.6% (1.28:1)	12, 22 (42%)/35, 45 (22%)	1.76	0.07%

Tooth numbers are indicated by the FDI two-digit system.
[a] Percentage of total missing teeth.
[b] Subjects are clinical patients.
[c] White.
[d] Negro.

Table 2 Syndromic and non-syndromic forms of tooth agenesis and the genes responsible.

	Responsible genes	Mouse models
Syndromes		
Down syndrome	Trisomy21	
X-linked HED	*Eda* [50]	*Tabby* [68]
Autosomal-dominant or -recessive HED	*Edar* [51] *Edaradd* [52]	*Downless* [51] *Crinkled* [52]
HED with immune deficiency	*Nemo* [53]	
Incontinentia pigmenti	*Nemo* [53]	*Nemo*−/− [70]
Witkop syndrome	*Msx1* [54]	*Msx1*−/− [34]
Rieger syndrome (Type 1)	*Pitx2* [55]	*Pitx2*−/− [72]
EEC3 syndrome	*p63* [56]	*p63*−/− [73,74]
AEC syndrome	*p63* [57]	
ADULT syndrome	*p63* [58]	
LMS	*p63* [59]	
Holoprosencephaly 3	*Shh* [60]	*Shh*−/− [75]
Van der Woude syndrome	*Irf6* [61]	
Non-syndromic	*Msx1* [28,35–38] *Pax9* [2,27,42–45] *Axin2* [47]	*Msx1*−/− [34] *Pax9*−/− [41]

HED: hypohidrotic ectodermal dysplasia; EEC: ectrodactyly, ectodermal dysplasia, and cleft lip/palate; AEC: ankyloblepharon–ectodermal defects–cleft lip/palate; ADULT: acro-dermato-ungula-lacrimal-tooth; LMS: limb-mammary syndrome.

A single base insertion producing frame-shift mutation in the paired domain of *PAX9* was originally identified in a family exhibiting lack of most permanent molars [2]. Affected members had a normal primary dentition. So far, several mutations [27,42–45] and polymorphisms in the promoter region [46] of *PAX9* gene have been identified in association with variable forms of oligodontia.

Genetic linkage and mutational analysis of a Finnish family with autosomal-dominant oligodontia has demonstrated a mutation in *Axis inhibition protein 2* (*AXIN2*) [47]. This mutation has also been associated with colorectal cancer. The protein product of *AXIN2* gene is a negative regulator of the *Wnt*-signaling pathway. Other researchers have identified several novel polymorphisms of *AXIN2* which may be a risk factor for selective tooth agenesis [48].

3.2. Associated syndromes and systemic diseases with tooth agenesis

Tooth agenesis is a primary feature of many syndromes that affect not only teeth but also several other ectodermal derivatives. The Online Mendelian Inheritance in Man (OMIM) [49] lists more than 60 genetic syndromes that include tooth agenesis as part of their phenotypic spectrum of anomalies. The candidate genes have been identified for many of these conditions (Table 2). The absence of maxillary central incisor, canine, second molars and especially first molar is rare in hypodontia. When these teeth are absent, it is more frequently seen in association with severe syndromic forms.

Down syndrome (trisomy 21) patients have a high prevalence of hypodontia. The reported prevalence rate was 63% and the most frequently absent teeth were the lower lateral incisors in Japanese patients with Down syndrome [62]. Other researchers have reported that hypodontia was present in 38.6% of patients and the teeth most often missing were the upper lateral incisors in Croatia [63]. There seems to be racial differences among patients with Down syndrome.

Patients with cleft lip and palate have a higher prevalence of tooth agenesis. The maxillary lateral incisor in the area of the cleft is the most commonly affected in both the primary and permanent dentition. Prevalence rates of 36–57% have been reported in Japanese patients [64]. Mutations in *MSX1* are often associated with non-syndromic cleft lip and/or cleft palate [65,66]. Van der Woude syndrome is an autosomal-dominant disorder affecting cleft lip, cleft palate, hypodontia, or pits and/or sinuses of the lower lip [67]. Kondo et al. [67] found a nonsense mutation in the *interferon regulatory factor 6* (*IRF6*) gene in the affected twin of a pair of monozygotic twins who were discordant for Van der Woude syndrome.

Ectodermal dysplasia refers to a heterogeneous inherited disorder characterized by, variable defects in the morphogenesis of ectodermal structures including hair, skin, nails, sweat glands, and teeth. Hypohidrotic ectodermal dysplasia (HED), a congenital disorder of teeth, hair, and eccrine sweat glands, is usually inherited as an X-linked recessive trait and caused by mutation in the gene encoding *ectodysplasin-A* (*EDA*) [50]. Autosomal-dominant and autosomal-recessive HED are rare and mutation in the *ectodysplasin anhidrotic receptor* (*EDAR*) [51] or the *EDAR-associated death domain* (*EDARADD*) [52] can cause these forms of the disorder. Mutation in the *NF-κB essential modulator* (*NEMO*) gene, a downstream target of *EDA* signaling, has also been found to cause X-linked HED with immune deficiency [53]. Previous studies in model mice with HED by *tabby* [68], *downless* [51] and *crinkled* [52] indicated that the *Eda*-signaling pathway is involved in tooth development during the determination of the number of molars and their morphology. These mice exhibit high incidence of absence of third molars, and abnormal shape and decreased size of crown [69].

Incontinentia pigmenti is a disturbance of skin pigmentation that segregates as an X-linked dominant disorder and also associated with a variety of malformations of the hair, nails, eyes, central nervous system, and teeth. Incontinentia pigmenti is caused by mutations in the *NEMO* gene [53]. Unlike X-linked HED with immune deficiency, incontinentia pigmenti affects females and is usually lethal prenatally in males. Embryos of deficient mice die at E12.5—E13.0 from severe liver damage due to apoptosis [70].

The main features of Witkop syndrome (tooth-and-nail syndrome) are hypoplastic nails and hypodontia. *Msx1* knockout mice manifest defective development of oro-facial structures and nails, including an arrest of tooth development at the bud stage and clefts, symptoms typical of hypodontia and Witkop syndrome [33,54]. Genetic linkage and mutational analysis demonstrated that a heterozygous stop mutation in the homeodomain of *MSX1* cosegregated with the phenotype [54].

Rieger syndrome is an autosomal-dominant disorder characterized by malformations of the anterior segment of the eye, periumbilical skin abnormalities, maxillary hypoplasia, and dental defects, including microdontia and hypodontia [55]. Both the primary and secondary dentition is affected. A homeobox transcription factor gene, *Pitx2*-deficient mice show defective development of the umbilical cord and eye, and tooth-development is arrested at the tooth bud stage in the mandible and at the placode stage in the maxilla [71,72]. Semina et al. [55] isolated the novel homeobox transcription gene *PITX2*, which they designated *RIEG*, and identified six mutations in this gene in individuals with Rieger syndrome.

Mutations in *p63* gene are the cause of several autosomal-dominant genetic syndromes characterized by ectrodactyly, syndactyly, ectodermal dysplasia, facial clefts, and hypodontia. Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 (EEC3) [56], ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome [57], acro-dermato-ungula-lacrimal-tooth (ADULT) syndrome [58], and limb-mammary syndrome (LMS) [59] have mutations in *p63* gene. *p63* is expressed in many developing epithelial structures, including teeth and is essential for several aspects of ectodermal differentiation. *p63*-deficient mice show severe defects in stratified skin, the limbs are absent or truncated, and hair follicles, mammary glands, and teeth are absent [73,74].

Holoprosencephaly is a genetically and phenotypically heterogenous disorder involving the development of forebrain and midface. Anophthalmia or cyclopia is evident along with congenital absence of the mature nose. The less severe form features facial dysmorphism characterized by ocular hypertelorism, defects of the upper lip and/or nose, absence of the olfactory nerves or corpus callosum, and hypodontia. The role of *Sonic hedgehog* (*Shh*) was confirmed by the detection of point mutations in holoprosencephaly patients [60]. *Shh* encodes a signaling peptide which is present in the oral epithelium prior to invagination and in the tooth epithelium throughout its development. Reduction and then loss of *Shh* function in mouse results in a cap stage tooth rudiment in which the morphology is severely disrupted [75].

Some of inbred strains of mice have absence of the third molars. In particular, EL/Sea (EL) mice have 100% incidence of absence of the third molars without abnormal crown shapes of other molars or any generalized anomalies of appearance [76]. EL mice show the arrest of development of third molars in the late bud stage, and a major locus for absence of the third molar, designated *am3*, of EL has been mapped within an approximately 4 cM region of chromosome 3. *Lef1* locus located on this region is a strong candidate for hypodontia in EL mice [77]. *Lef1* is a cell-type-specific transcription factor and mediates the *Wnt* signaling pathway, which is known to be critical for the specification of cranial neural crest (CNC) cells and may regulate the fate diversity of the CNC during craniofacial morphogenesis. *Lef1*-deficient mice have shown developmental arrest of the tooth germ in the late bud stage [78]. Mutation or polymorphisms in *Lef1* gene might be the cause of absence of the third molars in EL mice.

4. Conclusion

Recent genetic studies provide information regarding many genes related to both syndromic and non-syndromic forms of human dental agenesis. However, the causes of the most common form of hypodontia, the third molars and incisor—premolar type, are still unknown. Association between *PAX9* promoter polymorphisms and hypodontia in human has been reported [46], therefore other promoter polymorphisms in genes involved in tooth organogenesis might be associated with these types of hypodontia. In addition, the different polymorphisms might be cause of differences in the prevalence of dental agenesis among racial populations. It is likely that other specific hypodontia genes still exist and will be identified in the future by contribution of molecular genetic researches in both human and mouse models.

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