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Review Article

Morphological variation of the maxillary lateral incisor

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Summary The maxillary lateral incisor is a variable tooth morphologically. This tooth frequently shows reduction in size, and also various alterations in shape, for example, peg-shaped, cone-shaped, barrel-shaped and canine-shaped. The lateral incisor variant can be analyzed by family studies and using twin models, and these approaches have shown that genetic, epigenetic and environmental factors can all contribute to variation in the trait. Discordance of the phenotype in monozygotic twin pairs could be explained by the following two hypotheses: (1) the embryological environment of monochorionic twin pairs who share the same placenta and chorionic membrane during the prenatal period may differ, (2) phenotypic variation may be caused by epigenetic influences. Possible developmental factors are discussed in this review. Recent studies suggest that *Msx1*, *Pax9* and *Axin2* genes predispose to lateral incisor agenesis. Tooth reduction and agenesis seem to represent inter-related complex multifactorial traits, influenced by a combination of gene expression and function, environmental interaction and developing timing. Thus, accumulation of large data banks of morphological data is needed to support and clarify ongoing molecular genetic studies of dental development.

Contents

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1. Introduction

The maxillary lateral incisor is a variable tooth morphologically. This tooth frequently shows reduction in size [1,2], but it can occasionally be as large as the central incisor [3,4]. It also frequently shows different crown shapes, for example, peg-shaped, cone-shaped, barrel-shaped and canine-shaped [1,2]. Interruption grooves and deep lingual pits are also found more frequently on the lateral incisor than the central [1,2]. Reduced size or shape of the maxillary lateral incisor reflects the interaction of genetic, epigenetic and environmental factors [5—9]. In this paper we describe some genetic studies of reduced crown form in maxillary lateral incisors, and discuss some developmental aspects.

2. Frequencies of occurrence of crown reduction in the maxillary lateral incisor

Reduced crown form in maxillary lateral incisors has been reported to occur in from 0 to 10 percent of individuals in various populations but the anthropological interrelationships of the different lateral incisor variants remain obscure [10]. It has been thought that lateral incisor variants are intermediate in form between normal and congenitally missing teeth [11]. The third molar is most frequently absent in the permanent teeth, followed by the mandibular second premolar [12]. In a Japanese population, agenesis of the maxillary lateral incisor was ranked third, but its frequency of absence (1.32—1.33%) was about half that of the mandibular second premolar (2.84—3.26%) [13]. This result is consistent with meta-analyses of the prevalence of dental agenesis for many human populations from all over the world [14,15]. Thus, the maxillary lateral incisor shows a relatively common tendency to reduction in crown size, but its frequency of congenital absence is low. In contrast, the mandibular incisors are found to be congenitally absent relatively frequently, but reduced form of these teeth is rarely seen [2]. These facts suggest that crown reduction and congenital absence of a tooth do not necessarily appear at the same pace.

3. Genetic analysis of maxillary lateral incisor variants

The influence of genetic factors on missing maxillary lateral incisors has been analyzed by family studies that have shown a genetic influence on this trait, but have not been able to discover any evidence of a single gene being involved [16,17]. The expression of this trait is best explained by a polygenic, multifactorial model, and non-syndromic simple hypodontia and tooth size can be considered as representative dental quantitative traits [8,18]. It is considered that other maxillary lateral incisor variants are also likely to be best explained by a polygenic model.

Kondo et al. [7] have reported the findings of a genetic analysis that focused on maxillary lateral incisor variants in a sample of Japanese twins (Figs. 1 and 2). The classical twin model, where similarities in monozygotic twin pairs are compared with similarities in dizygotic twin pairs, is very useful to clarify the contribution of genetic and environmental influences to variation in the size and shape of teeth. Monozygotic (MZ) twin pairs are assumed to share all the same genes whereas dizygotic (DZ) twin pairs only share 50% of their genes on average, similar to other sibling pairs. Various twin research study designs, including comparisons of the similarities within MZ and DZ twin pairs, have enabled researchers to further quantify the relative contributions of genetic, epigenetic and environmental factors to variation in maxillary lateral incisors [6].

Among 1005 twin pairs, a reduced form of the maxillary lateral incisor was seen in 121 twin pairs [7]. In this study, a reduction was defined as being present if it was seen in at least one side of either member of a twin pair. The reduction was divided into size and shape elements, so that these features could be assessed separately. Size was classified into three types by calculating the ratio of the crown sizes of the lateral incisor compared with the central incisor as follows: normal (>80%), small (70.0—79.9%) and diminutive (<70%). Shape was classified as normal, canine-shaped, peg-shaped and cone-shaped. Anything other than normal shape was considered to represent an example of the reduced trait. Concordance rates of the reduced form between right and left sides, and between co-twins of a pair were calculated.

The concordance rates between right and left sides ranged from 52.5% to 71.9%, and were not significantly different between MZ and DZ twin pairs (Table 1). The concordance rate between twin pairs was significantly larger within MZ twin pairs than within DZ twin pairs (Table 2), suggesting a genetic basis to variation but environmental and/or epigenetic factors were considered to also be important because the percentage concordance within MZ twin pairs was only 50—60%. Since the concordance rate within MZ twin pairs was larger for the size element than for the shape component, it is possible that hereditary factors influence tooth size more strongly than shape, but more sophisticated

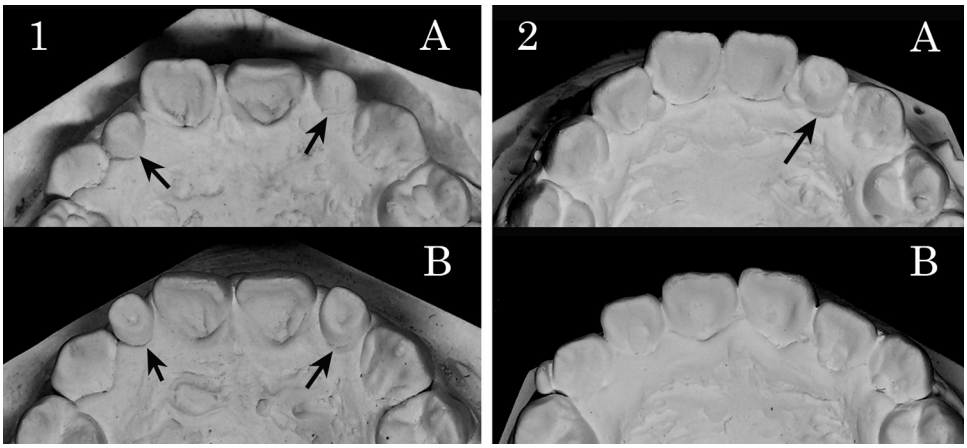

Figure 1 Two cases of maxillary lateral incisor variation in male MZ twin pairs. (1) All four lateral incisors from right and left sides of two members of a twin pair were reduced in size and were peg-shaped (arrows). Apparently, the dental morphology was more affected by genetic factors than by environmental factors. (2) Only one of four teeth was reduced in size and was peg-shaped (arrow). In this case, apparently the dental morphology was more affected by environmental factors and/or epigenetic factors than by genetic factors.

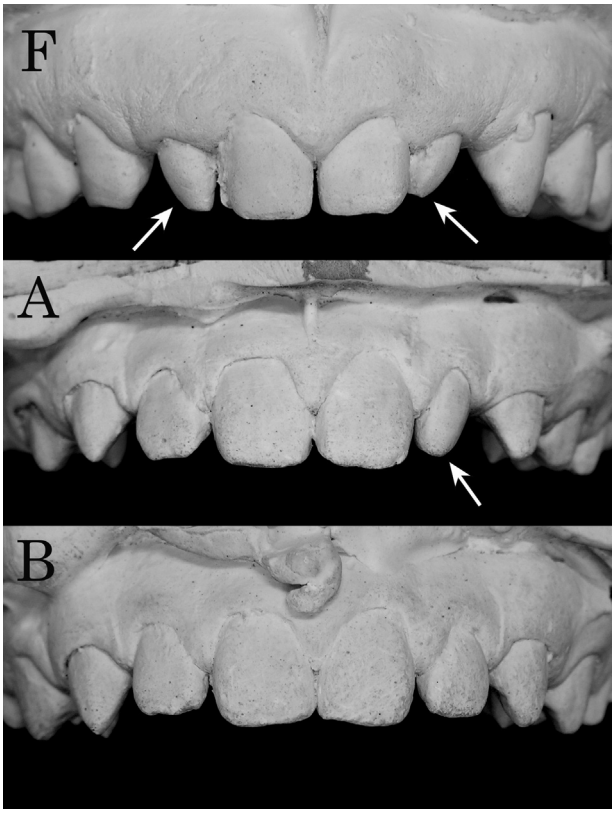

Figure 2 An example of maxillary lateral incisor reduction in a pair of male MZ twins and their father (labial view) In the father (F), the lateral incisors on both right and left sides were reduced in size and conical-shaped (arrow). In twin A, only the left side (arrow) was reduced. In twin B, both sides were normal in size and shape. The lateral incisor variants in this case are apparently influenced by heredity factors but also by environmental and/or epigenetic factors.

Table 1 Concordance rates of lateral incisor reduction between right and left sides.

		MZ		DZ	
		Size	Shape	Size	Shape
Sample number					
Concordant	(++)	41	31	13	8
	(−−)	31	29	10	17
Discordant	(+−)	16	28	9	7
Total		88	88	32	32
Concordance rates[a]		71.9%	52.5%	59.1%	53.3%

Reproduced from Kondo et al. [7].
(+) Indicates reduced form, and (−) indicates normal.
[a] Concordance rate indicates $(++)/\{(++)+(+-)\}\times 100$.

Table 2 Concordance rates of lateral incisor reduction between members of a twin pair.

		Size		Shape	
		MZ	DZ	MZ	DZ
Side numbers[a]					
Concordant	(++)	73	18	59	9
	(−−)	56	12	59	26
Discordant	(+−)	37	33	48	28
Total		166	63	166	63
Concordance rate[b]		66.4%**	35.3%	55.1%**	24.3%

Reproduced from Kondo et al. [7].
(+) Indicates reduced form, and (−) indicates normal.
[a] The side number shows in the table as a sample number, not an individual number.
[b] Concordance rate indicates $(++)/\{(++)+(+-)\}\times 100$.
** $P<0.01$ (Chi-square test between MZ and DZ).

Table 3 Reduced tooth number on right and left sides in both members of twin pairs.

	Size		Shape	
	MZ	DZ	MZ	DZ
Pair number				
0[a]	20	2	16	9
1—3	28	22	43	19
4	29	7	18	3
Total	77	31	77	31
Percentage of 4 teeth (exclude 0 tooth)	50.9%*	24.1%	29.5%*	13.6%

Reproduced from Kondo et al. [7].

[a] This table shows the number of reduced lateral incisors, when there was evidence on at least one side and in at least one co-twin, for either size reduction or shape reduction, or the reverse relationship.

* $P < 0.05$ (Chi-square test between size and shape).

genetic modelling approaches would be needed to explore these relationships further. Since considerable phenotypic variation is found in the reduced lateral incisor, tooth shapes within MZ co-twins can be very similar or quite different, as Saheki [19] noted. Table 3 shows the frequency of reduced maxillary lateral incisors when considering all four teeth in both members of a twin pair. All four teeth showed the reduced type more frequently in MZ twin pairs than in DZ twin pairs ($P < 0.05$).

4. Discordance of phenotypic expression in MZ co-twins

Discordance of reduced tooth form in the maxillary lateral incisor between co-twins of MZ pairs has been discussed from genetic, epigenetic and environmental perspectives. In this paper we consider two hypotheses: (1) environmental factors influencing tooth formation, and (2) phenotypic variation caused by epigenetic influences.

4.1. Is the embryonic environment identical for both members of an MZ twin pair?

Townsend et al. [20] have discussed discordance between MZ co-twins due to differences in their embryonic environment. Monochorionic twins are MZ twins who share the same placenta and chorionic membrane during prenatal development. Although the twins have a common placenta, their blood supply is usually well-balanced [21]. However, in 5—15% of monochorionic pregnancies, twin transfusion syndrome associated with anterio-venous anastomoses, can lead to one member of a twin pair receiving better nourishment than the other. Differences in blood flow to developing tooth germs at critical stages of their formation, resulting in nutritional discrepancies, could presumably also influence the resultant dental phenotypes. This could lead to one member having well-developed lateral incisors, but the other having less-developed lateral incisors. For example, uptake of glucose into dental epithelial and mesenchymal cells, mediated by glucose transporters, has been shown to play an important role in early dental development and subsequent determination of tooth size in mice [22].

4.2. Epigenetic influences may explain discordance between MZ co-twins

Townsend et al. [23] noted that there was evidence of one missing maxillary lateral incisor or mandibular second premolar in 24 of the 278 MZ twin pairs who they examined, with 21 of these pairs showing discordant expression (87.5%). By focusing on the differences between MZ co-twins rather than their similarities, they postulated that epigenetic events during odontogenesis might account for the distinct differences between members of MZ twin pairs. Epigenetics refers to heritable changes in gene activity that are not caused by changes in the DNA sequence [24,25]. Variation due to genetic influences is classically based on changes to the DNA sequence (the genotype), but alterations in gene expression or alterations in the nature of cellular interactions at a local tissue level, both of which can be referred to as epigenetic factors, have other causes.

The science of epigenetics includes the many regulatory systems of the body involving DNA methylation and histone modification. Although twins are epigenetically indistinguishable during the early years of life, older MZ twins can exhibit quite remarkable differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation, affecting their gene-expression portrait [26,27]. This fact indicates that tooth formation of the later-developed maxillary lateral incisor may be more likely to be affected by epigenetic influences than the early developing teeth.

5. Developmental factors for the maxillary lateral incisor variant and agenesis

Butler [28] was a pioneer in describing the concept of morphogenetic fields to account for the gradients in size and shape of teeth evident in the dentitions of different species (reviewed by Townsend et al. [29]). Dahlberg [30,31] adapted Butler's concepts to the human dentition and proposed that there was a field of influence operating on each of the tooth classes. The key tooth in each tooth class is considered to be the most stable tooth compared with the other more variable teeth. Butler's field concept has been re-interpreted in the light of recent molecular findings [32—34]. An odontogenetic homeobox code model of tooth patterning has been developed from studies in mice proposing that certain genes play specific roles in morphogenesis for each incisor and molar pathway. However, the mouse dentition is highly specialized with a long toothless diastema region instead of canine and premolar teeth, so some care is needed when translating findings to humans. Yamanaka et al. [35] used an insectivora (house shrew, *Suncus murinus*) as a model for mammalian heterodonty because it displays all tooth classes, and they showed that *Sonic hedgehog* expression localized to the presumptive tooth-forming regions for each tooth class.

Sofaer et al. [36] discussed tooth reduction over the course of human evolution. Reduction in size of the jaws during hominid evolution has been accompanied by a general

reduction in tooth size, and the reduction process appears to be more rapid in the most posterior teeth of each jaw. In each tooth class, the most posterior member starts to develop after the most anterior member, with exception of the mandibular incisors. Therefore, the most posterior tooth of each class reflects the effects of variation in the amount of available space.

Brook and colleagues [8,37] have suggested that the different prevalence of anomalies in different regions of the dentition could be associated with developmental timing, later-developing teeth displaying more variability than early-developing teeth in the same class. The maxillary lateral incisor is the most posterior and latest developed tooth in the incisor region, and its greater variability is likely to be due to a greater environmental influence on variation [38].

The maxillary lateral incisor forms in the location of the boundary between the premaxillary (primary palate) and maxillary processes [39], and this local factor may relate to the greater variability of the lateral incisor in both size and shape [20]. Interestingly, however, Mizoguchi [40] noted that the deciduous lateral incisor was as stable as the central incisor in size. He speculated that the deciduous incisors had some important function which was not shared by the permanent incisors but was required during the infant period when only the deciduous incisors were present. Although the number of congenitally missing teeth tends to be substantially greater in the permanent dentition than in the primary dentition, the most frequently missing teeth in the primary dentition are the incisors, while the premolars of the permanent dentition are most commonly absent, if one excludes the third molar teeth [41].

5.1. Compensatory interactions between teeth

The early-developed tooth tends to behave as an environmental factor for the adjacent later-developing tooth [42]. Grüneberg [43] stated that if the first molar of the mouse, which was the largest and the earliest developed in the molar row, was reduced, then the second and third molars tended to grow larger than in a normal mouse. Sofaer et al. [44] showed that when a lateral incisor was missing on one side, the central incisor adjacent to the missing tooth tended to be larger than the central incisor on the other side. These researchers also proposed that agenesis of a tooth might lead to an increased growth potential of neighbouring teeth, reflecting a compensatory effect in growth of adjacent developing tooth germs.

Hanihara [3] analyzed the relationship in the mesiodistal crown diameters between the maxillary lateral incisor and the other permanent teeth, and showed the size of lateral incisor was highly correlated with the size of the other teeth, i.e. when the lateral incisor is reduced, remaining teeth also tend to be reduced. Garn et al. [45,46] showed that agenesis of the third molar tooth was not an isolated anomaly, but rather a polymorphism related to the frequency of other missing teeth.

Mizoguchi [47] tested the compensatory interaction hypothesis by using path analysis in a Japanese population and he concluded that there was no, or little, compensatory growth of the later-developing teeth in the tooth row from central incisor to second molar in each jaw, but only the third molar grew to compensate for a whole dentition of certain length. Yamada et al. [48] demonstrated that tooth size of the remaining teeth was greater in a sample with third molar agenesis than in a group where all four third molars were present, with the exception of the maxillary lateral incisor. Their results could be explained to some extent by compensatory interactions within molar tooth row, but it is interesting that the maxillary lateral incisor was reduced in individuals with third molar agenesis. Thus, the maxillary lateral incisor and the third molar are reduced synchronously. There is a tendency for the size of remaining teeth to be more reduced as the number of missing teeth increases, but tooth size in individuals with one or two teeth missing is generally larger than in individuals with all 32 permanent teeth [49]. These findings indicate that the relationship between agenesis and the sizes of remaining teeth is likely to be complex.

Kondo and Hanamura [4] analyzed the mesiodistal crown diameters of the maxillary incisors and first molars in 301 Japanese individuals, and examined the existence of compensatory tooth size interaction between the early-developed central incisor and the later-developed lateral incisor. The central incisor and first molar in the group that had reduced lateral incisors were not smaller than those in the other groups who had normal or large lateral incisors. Thus, the reduced lateral incisor did not always lead to the reduction of the other teeth. The central incisor was larger in the group who had reduced lateral incisors than in the group who had normal-sized lateral incisors. This result indicates that the size of the lateral incisor was likely to reflect a compensatory response related to a large central incisor.

Fluctuating asymmetry in size of the lateral incisor was greater in the reduced lateral incisor group than in the normal lateral incisor group. Compensatory growth of the lateral incisors was noted in those groups where the lateral incisors showed strong asymmetry in their size and also in the group who displayed reduced lateral incisors. It was suggested by the authors that the compensatory growth was related to right and left side asymmetry in the lateral incisor. Correlations among teeth in the same tooth class, and correlations between right and left sides of the same tooth, were relatively high but the correlations among other tooth classes were low. It was thought that the reduction and compensatory growth of the lateral incisor were limited within the same tooth class, but rarely influenced the whole tooth row. In conclusion, it is proposed that reduced maxillary lateral incisors grow to compensate for the size of the adjacent central incisor in some cases, but their reduction also reflects reduction of the whole dentition in other cases (Fig. 3, Table 4).

5.2. Inhibitory cascade model

Kavanagh et al. [50] constructed an inhibitory cascade model by uncovering the activator-inhibitor logic of sequential tooth development. Their hypothesis was based on experiments of tooth development in the laboratory mouse and supports the important role of epigenetic influences during odontogenesis. Mouse molars develop sequentially and the dental lamina, extending posteriorly from the developing first molar, gives rise to the second molar. When the

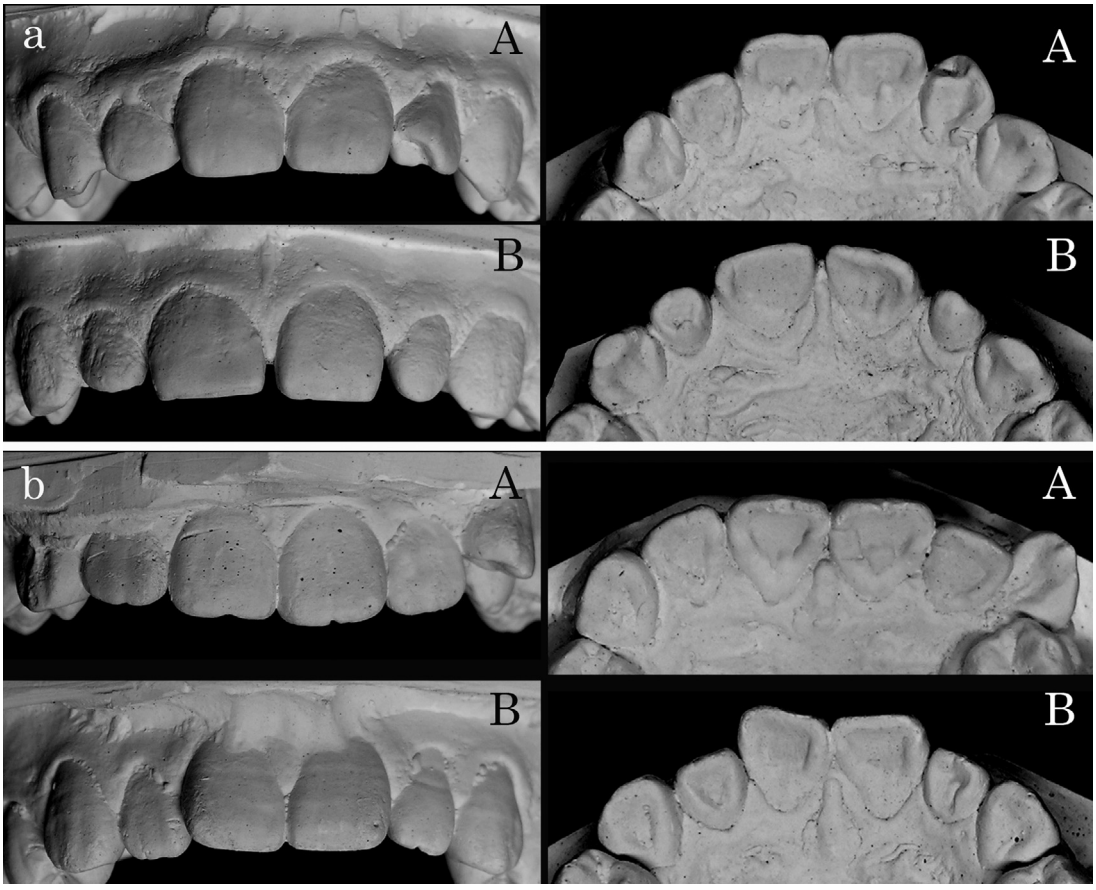

Figure 3 Two cases of twin pairs displaying compensatory growth in maxillary incisors. In both cases, the lateral incisors of twin B are reduced in size. Mesiodistal crown diameters are shown in Table 4. (a) Male MZ twin pairs: Twin B has larger central incisors than twin A, and the lateral incisors are reduced in size, but the first molars are almost the same size. In twin B, there is evidence of compensatory interaction between the central and lateral incisors. (b) Female DZ twin pairs. Twin B has smaller central and lateral incisors, and first molars than twin A. The whole dentition is reduced in twin B.
Reproduced from Kondo and Hanamura [4].

second molar was cultured apart from dental lamina of the first molar, the second molar developed faster and grew larger than in the intact situation. These authors proposed that the mesial molars inhibit development of the distal molars. This model explains the relative size of mandibular molars by a balance of inhibitor and activator substances, and predicts evolutionary patterns in the dentition. The model has been tested from both paleontological [51,52] and comparative anatomical [53] perspectives.

In a study of delayed erupted maxillary first molars, Rasmussen used the term ''9-year-molar'' [54]. The eruption times of the teeth reported were between that of the first

Table 4 Tooth dimensions of two cases of twin pairs in Fig. 3 (mm).

	Right side			Left side		
	M^1	I^2	I^1	I^1	I^2	M^1
a						
A	10.55	6.90	9.25	9.10	7.25	10.50
B	10.65	5.80	10.10	9.75	6.10	10.55
Difference between A and B ($A - B$)	−0.10	1.10	−0.85	−0.65	1.15	−0.05
b						
A	10.95	7.45	8.90	9.05	7.55	11.10
B	10.35	5.25	8.25	8.30	5.80	10.25
Difference between A and B ($A - B$)	0.60	2.20	0.65	0.75	1.75	0.85

Reproduced from Kondo and Hanamura [4].

and second molars, and the morphological configurations were found to be closest to that of the second molar. This led to the question ''Are the aberrant teeth really first molars?'' Yamada [55] reported similar cases, and thought that the aberrant teeth were early-developed second molars. The inhibitory cascade model is useful in interpreting these cases, as a congenitally missing first molar would lead to altered development of the second molar.

The inhibitory cascade model could also be applied to the incisor region, e.g. when the early-developed central incisor is large, development of the later-developed lateral incisor may be inhibited, so that the lateral incisor will tend to be reduced in size.

6. Molecular genetics of tooth agenesis

Non-syndromic tooth agenesis includes different phenotypes: hypodontia is the term used for congenital absence of one to six teeth excluding third molars; oligodontia refers to the absence of more than six teeth excluding third molars; and all teeth are missing in anodontia [56,57]. The molecular basis of agenesis is not completely understood, despite identification of several mutations in *Msx1* and *Pax9* genes that seem to be crucial for tooth agenesis, and mutation in the *Axin2* gene that causes oligodontia together with a predisposition to colo-rectal cancer (reviewed by Matalova et al. [56] and Shimizu and Maeda [57]).

Msx1 and Pax9 are transcription factors necessary for normal tooth development. *Msx1* is a member of the muscle segment homeobox family, members of which are repetitively expressed during organogenesis. *Pax9* plays an important role as a regulator of cellular pluripotency and differentiation during embryonic patterning and organogenesis and also in post-natal life. The protein product of the *Axin2* gene is a negative regulator of the *Wnt*-signalling pathway. The *Wnt*-signalling pathways are signal transduction pathways made of proteins that pass signals from outside a cell through cell surface receptors to the inside of the cell.

A case—control study with the largest number of genes and single-nucleotide polymorphisms assessed in the same population was performed recently to identify the causes of maxillary lateral incisor agenesis [58]. No significant allelic genotypic or haplotypic associations were found regarding *Axin2*, *TGFA*, and *Msx1* genes, but two strong significant interactions between *TGFA-Axin2* and *Msx1-TGFA* were revealed. *Pax9*, *EDA*, *Spry2*, *Spry4* and *Wnt10A* were noted as risk factors for maxillary lateral incisor agenesis. These results suggest that genes involving hypodontia and/or oligodontia are also involved in maxillary lateral incisor agenesis.

Advances in molecular genetic analysis may identify candidate genes that participate not only in maxillary lateral incisor agenesis but also in its reduction. In recent years, the progress of gene studies has been remarkable, but understanding of the morphological expression of traits is also important. Tooth reduction and agenesis appear to represent a complex multifactorial phenotype, influenced by a combination of gene function, epigenetic influences, environmental interaction and developing timing [59]. While this paper has focused on anthropological evidence to support the influence of genetic, epigenetic and environmental factors on the development of maxillary lateral incisors, it is clear that studies based on both molecular biology as well as anthropology are needed to provide further insights into the interactions between these factors during odontogenesis [60]. For example, accumulation of large databases of human dental morphological data is needed to support the molecular genetic studies that are being carried out using experimental animals.

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Conflict of interest

None.

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