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Research Article

A Pathogenetic Model For The Origins And Locations Of Idiopathic Supernumerary Teeth.

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Running head: Pathogenesis of Supernumerary Teeth

Abstract

The origins and localizations of idiopathic supernumerary teeth are much debated. However, idiopathic supernumeraries can be explained by a combination of localized anterior premaxillary factors and a general dental lamina effect that may also involve normal teeth. Midface Sonic hedgehog (SHH) signaling induces mesiodentes and tuberculate incisors, potentiated by midline developmental weaknesses and genetic variants. SHH can affect morphology, with complex tuberculates from longer primary dentition exposures, but simpler secondary mesiodentes with crown inversions and palatal placements that reflect gradients. Such local factors are minimized with multiple supernumeraries (5 or more), showing other effects more clearly. Here, laminal layer growth differences cause inductive morphogen "sinks" through buckling at stress points, which is greatest at mid-lamina and least at the ends, and increasing with length. Dental lamina sectional differences in these parameters explain more mandibular than maxillary multiples, relatively few incisors, premolars as commonest in the lower jaw, and molars in the upper. Terminal laminal buckling with supplemental teeth at the end of incisor and molar series is unexpected, but teeth develop as groups, and a correctly oriented supernumerary may develop normally and displace a series, while end position vulnerabilities cause distortions of an otherwise normal tooth.

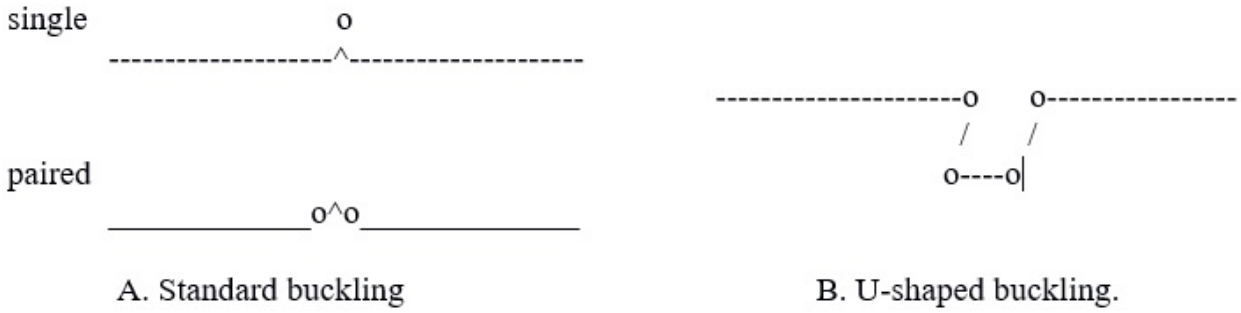
Keywords : *Buckling; dental lamina; premaxilla; Sonic hedgehog; supernumerary teeth.*

INTRODUCTION

Supernumerary teeth (ST) are the most common human malformations, with likely rates of 2.4- 6%, "or possibly even higher."[1] Although causally heterogeneous, with some genetic forms,[2] most are idiopathic without other findings, highly variable, and can be categorized by numbers, location, morphology, and other factors.[3]

Here, a dual pathogenic model for idiopathic ST is presented with 1. A general mechanism involving the entire dentition as mechanical stress related dental lamina buckling gives disruptions that create a focus for tooth initiation (Figure 1). This may also influence normal tooth induction. 2. Localized premaxillary effects with midface induction by Sonic hedgehog (SHH)[4] and a specific midline vulnerability.[5,6]

Figure 1. Buckling and tooth bud initiation. o = new tooth bud in disrupted area.



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These mechanisms explain multiple observations of ST, including male biases,[7] frequent mesiodental crown inversions and palatal placement,8 more multiples in the mandible, relatively few in the incisors, premolars as the most common in the lower jaw, and molars as the most common in the upper.[9,10,11]

MATERIALS AND METHODS

Literature review analysis limited to idiopathic ST without facial clefts, syndromes, or a positive family history. Wisdom teeth and odontoma are excluded. As few as 2 ST have been labeled multiples,[12,13] but 5 or more are typically cited, a confusing designation with up to four teeth defined as isolated! However, this is entrenched in the literature and, for consistency, this cutoff and isolated and multiple are used in this sense here. Premaxillary ST include three standard types (**Table 1**), with great morphological variability: Mesiodens can be tuberculate in form, tuberculates can be conical, and supplementals can be of both shapes as well as normal.[14]

Table 1. Types of isolated premaxillary ST. After Garvey et al.[15].

Type	Typical Morphology	Typical Location	Dentition
Mesiodens	Conical. Pairs common	Between central incisors palatal and inverted	Secondary
Tuberculate	> one cusp or tubercle, Barrel-shaped.	palatal aspect of central incisors	Primary
Supplemental	Duplication in normal series	end of a tooth series, esp, maxillary lateral incisor	Secondary

SUPERNUMERARY CHARACTERISTICS

Epidemiologies vary, reflecting methodological considerations and population differences. Radiographs are needed to detect unerupted examples, and rates vary with age,[3] with ST about three times more common in permanent dentition. New ST can appear for decades,[9] and mesiodentes, the most common type, may be resorbed over time.[16] Panoramic radiographs showed ST frequencies of 1.2- 3%, and data suggested 2.4-6%, "or possibly even higher."[1] With this, statistics need to be regarded as rough estimates highly dependent upon context.

Most ST are single, and frequencies rapidly decrease as numbers rise: Rajab and Hamdan[17] noted one extra tooth in 77% of cases, 2 in 18·4%, and 3 or more in 4·6%, while Açikgöz et al.[18] found only 0.06% with 5 or more.

Mesiodentes, typically the most common type (although not in the series of Brinkmann et al.[19]), are exceptional with multiples, and premaxillary ST predominate with 4 or less: In large series (over 100 patients) Herath et al.[20] found 94.94% of ST in the premaxilla, De Oliveira Gomes et al.[21] 86.7%, and Rajab and Hamdan[17] 90% (92·8% of these in the central incisor region). While most multiples were mandibular, 95% of patients with multiples had ST in both jaws,[9,10,11] supporting a generalized process instead of localized effects with isolated supernumeraries.

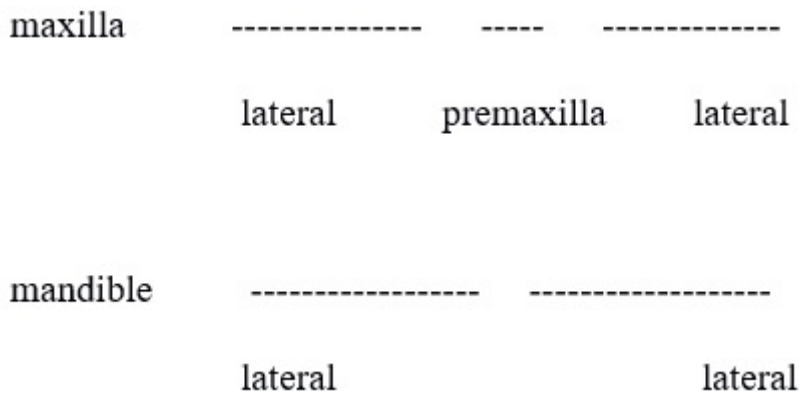
BUCKLING AND INITIATION

Biologically, buckling, an acute structural deformation from mechanical stress, arises from growth differentials in adherent tissue layers, creating structures such as intestinal loops and cerebral cortex convolutions. There can be secondary effects- gut constraints on epithelial growth cause villus morphogenesis, and also localize stem cells to crypts as "undulations create sinks for morphogens that are secreted by the epithelial cells, leading to a concentration gradient along the length of the villus. So… constrained growth of the epithelium not only directs its morphogenesis but also its pattern of differentiation."[22]

And here, aberrant buckling of the dental lamina, the source of normal tooth buds, may create similar morphogenic field distortions[23] capable of initiating extra teeth.

The lamina originates in five separate areas (**Figure 2**). Epithelial invaginations into mesenchyme[24] form two adherent linear layers where complex interactions affect tooth size, number, and morphology.[25] Different molecular signals in the two layers[26] indicate possibilities for different growth rates primed for buckling.[22] At the same time, disruption of the dental lamina can induce additional teeth, as with oral clefts.[27]

Figure 2. Dental laminae relative sizes and locations (not to scale).



Other factors being equal, mechanical stress is greatest at the middle of a structure and least at the ends, and increases with length.[22] Local variations and inhomogeneities can modify this, and lateral asymmetries could produce labial or palatal displacements. U-shaped buckling is also consistent with rosettes, "a classical clustered flower like presentation"[9] (**Figure 1**).

More mesenchyme increases tooth numbers,[25] so a shorter lamina should show fewer and smaller teeth, and longer more and larger. And here,[27] suggested human tooth size as a normally distributed genetic trait correlates with most number variations, larger with extra, and smaller with missing, teeth. Male teeth tend to be larger, and ST biased, as seen with mesiodentes,[28,29] anterior maxillaries,[30] premolars,[31] and multiple ST (below), but absences tend to be female.[32]

Dental lamina buckling can include later effects as well. With mesenchymal invagination, the epithelial bud forms a folded cap, where a model of buckling from differential growth of adherent layers can explain cap shape, with specific parameters determining the number of invaginations.[33] After this, Osborn[34] noted how "Cells at the growing soft tissue interface between the ectoderm and mesoderm in a tooth anlage are observed to buckle and fold into a template for the shape of the tooth crown." A computer model based upon directional constraints that "force the growing epithelium to buckle and fold" could generate the number and shape of tooth crown cusps, and explain evolutionary changes. Marin-Riera et al.[35] further extend these approaches.

With this, factors enhancing laminal buckling could affect tooth number and morphology together, with simple conical and complex tuberculate morphologies as opposite ends of a spectrum of fine scale laminal responses associated with grosser effects on tooth initiation (below).

Human teeth are also usually symmetrical, often remarkably so: In a cone-beam computed tomography study, for the first and second molars in both jaws, the root and canal morphology of specific teeth "showed perfect symmetry" in over 70% of cases when both were present.[36] With this, and a generalized mechanism (above), bilaterally symmetrical ST are not unexpected.

Finally, buckling mechanics should interact with molecular tooth initiation. SHH involvement is noted in the next section, but other genes implicated with syndromic supernumeraries2 may also affect buckling through differential growth effects.

THE PREMAXILLA

While buckling can occur throughout the dentition, unique premaxillary factors also affect isolated ST. Mesiodentes, generally the most common ST type, are limited to the central maxillary incisor gap, and reflect several factors.

First, there is SHH midface induction. Here, "Pathway activity is detected in the medial nasal processes that contribute to the median aspect of the upper lip and primary palate, as well as the maxillary processes that give rise to the lateral aspects of the upper lip and the secondary palate."[37]

Anatomically, the upper incisors are all adjacent to the premaxilla, paired bones fused anteriorally, with an incisive fossa posteriorly. They are also adjacent to the median palatine process/primary palate. Therefore, for teeth, the maxillary incisors are associated with the highest concentrations of SHH and should be particularly vulnerable to variations in levels.

Premaxillary effects from deleterious mutations correlate with incisor morphology, ranging from a single central incisor with minor changes, to total absence with agenesis, while canines arise from separate fields[27] and are unaffected. Asymmetric signaling from the palatal side of the lamina would explain certain positional distortions: Radiographically, mesiodentes crowns were inverted in 67%, horizontal to the tooth axis in 6%, and normally directed in only 27%, while 89% were palatal against the dental arch, 11% overlapped the arch, and none were labial.[8]

Second, major contributions to mesiodentes from cooperative interactions between co-occurring genetic alterations, including "functionally enriched gene groups in the sonic

hedgehog... signaling pathways."[38] This could explain the rarity of mesiodentes with multiple ST, since those genes would be independently occurring factors. At the same time, although numbers are small, high mesiodentes rates with familial multiple ST ("Multiple ST Analysis: Methods," below) may reflect a more general molecular defect that affects other areas of dentition as well.

Third, a particular midline vulnerability to developmental disturbances[5] should create a susceptible area between the anterior maxillary incisors. This reflects midline topology as a null space between two mirror image developmental fields, resulting in the loss of positional information central to cell fate determination.[6]

This should be exaggerated by midline widening and, in fact, mesiodentes are associated with diastemata, broadened spaces between the central incisors.[39] Diastemata with or without mesiodentes with the Nance-Horan syndrome,[40] and frequent mesiodentes in Opitz G/BBB syndrome,[3] which involves midline widening, show that the gaps are not simply caused by the supernumeraries.

Buckling is also most likely at the middle of dental laminae which, for the premaxilla, is at the central incisor gap.

The last two vulnerabilities are absent in the mandible, which lacks a middle lamina (**Figure 2**). Without a similar relationship to SHH induction. it bears a very different relationship to the midline, implying a considerably reduced risk for extra teeth, which is indeed the case.

(Incidentally, suggestions of mesiodentes as a holoprosencephaly microform rest upon one mother with mesiodens and an affected child with no detectable mutation.[42] This seems unlikely, with a dearth of reports of this common dental finding in mutation carriers, while midline narrowing with holoprosencephaly should actually decrease rates.)

Another type of ST, tuberculates, are on the palatal aspect of central incisors, with more than one cusp or tubercle, generally barrel-shaped, often paired, and sometimes invaginated.[15] Clustering around the midline suggests buckling, but associated diastemata seem to be absent, going against positional information effects. However, palatal placement supports midface SHH inductive effects.

Differences from mesiodentes may reflect timing: simple conical mesiodentes are in the secondary dentition, while tuberculates are primary, giving a longer/stronger exposure to SHH signaling for a more complex structure.

Finally, supplemental duplications at the end of a tooth series may be morphologically normal. They are most common at the maxillary lateral incisor, again consistent with SHH effects here, but also appear elsewhere, as with distomolars at the end of the molar series.

Buckling in both locations should be unlikely at the ends of lamina segments, but apparent aberrancies may be illusory. Tooth series develop as coordinated units. In both Butler's field theory and the clonal theory, the two main suggested mechanisms, the same teeth are more stable in development, and the first upper incisors, second lower incisors, canines and first molars show the least amount of variation.[43] With this, the supplemental tooth at the end of a series may not be the actual supernumerary. That is, if an additional tooth is induced in normal alignment, as between the first and second molars, the developmental process will normalize it morphologically, giving a second molar, and laterally displacing subsequent teeth. With this, the most distal molar in the new series is probably the most sensitive to abnormal development, and most likely to be atypically shaped.[44]

PREDICTIONS AND EXPLANATIONS

The buckling hypothesis can explain a variety of observations, with specific predictions that can be tested against multiples generally unobscured by premaxillary factors:

1. With equal total lamina length, two longer segments in the mandible compared to shorter triplets in the maxilla mean more ST in the mandible.
2. A short lamina in the maxilla, and a mandibular location at an end of a laminal segment, would explain relatively fewer ST incisors.
3. Premolars at the mandibular laminae centers should be the most common ST in the lower jaw.
4. The center shifts with shorter lateral maxillary laminae, making molars most likely in the upper jaw.
5. Males, with longer laminae,[32] should have more multiples than females.

   Buckling can also explain some more general observations:
6. Longer laminae in the secondary dentition should mean more ST than in the primary.
7. Asymmetries perpendicular to the lamina should produce labial or palatal displacements,
8. Buckling variations can explain certain binaries and rosettes (**Figure 1**)

MULTIPLE ST ANALYSIS: METHODS

To test the above predictions, and better understand multiple ST epidemiology, cases were analyzed from three recent multiple ST reviews.[9,10,11] Criteria and definitions differed, and overlaps were common, but each study had unique cases. We used five as a minimal ST number, and excluded: 1.With a continuously hyperactive dental lamina,[9] as atypical; 2. An outlier with 22 ST,[45] the only instance of more than 17 in all; 3. Familial cases.[46,47,48] These are rare,[49] and probably heterogeneous. 4. A patient with more than the 6 maxillary ST50 that others cite, but without clear details. With this, 58 cases remained.

Some caveats: Again, figures should be regarded as estimates. Besides methodological and epidemiological issues, multiples are diverse, and local factors affect differentiation. Criteria vary, and segment based classifications blur premaxillary distinctions from nearby areas. To allow for this, superior canines with premaxillary findings are included as anterior. This introduces some inaccuracy, but canine ST are relatively infrequent with multiples, minimizing effects. Frequencies also have two different contexts with different causal implications: ST numbers, and patient rates; e.g, anteriors as 12% of ST, but 37% of patients.

There are also ascertainment and publication biases: More ST have increased dental problems, and are more impressive as case reports. As evidence, 25 out of 38 individual reports had more than 8 ST compared to only 3 out of 19 patients where several cases were reported together (see below).

MULTIPLE ST FINDINGS OF THE 58 CASES ANALYZED

1. There were 41 males and 15 females, plus 3 unspecified, for a 2.7:1 ratio.
2. Confirming separation from other multiples, mesiodentes were rare, with two solitary, and one quadruple in only three patients, which may be coincidental,. However, three solitary mesiodentes were seen in the five excluded familial cases, and all affected patients with mesiodentes in the excluded and included groups had more than ten ST, so some relationship with multiples is possible.
3. Both jaws had ST in all except 2 patients with maxillary findings only.
4. There were 233 maxillary and 290 mandibular ST. Excluding the 6 mesiodentes, 65 were anterior, with about as many in each jaw. Non-anterior ST were roughly 45% maxillary and 55% mandibular.
5. Anterior involvement (typically, without mesiodentes) in one or both jaws occurred in 32 patients (39%), who had about 12% of all supernumeraries by number.
6. There were roughly 82 molars and distomolars in 27 patients, the former about twice as common numerically, and perhaps a bit more common in terms of numbers of patients.
7. Canine involvement was obscured by consolidations with other groups, but seemed uncommon, and probably less frequent than distomolars.
8. Premolars were more common in the mandible, molars in the maxilla.
9. Isolated and multiple findings differed radically for the premaxilla: Mesiodentes, with the highest isolated rate, become the rarest, and the percentage of other incisor ST was about one fifth of the isolated rate. This supports differentiation of the premaxillary area from the rest of the dentition.

These findings confirm buckling predictions, and support a generalized process separate from the localized premaxillary factors involved with isolated ST.

ALTERNATIVE EXPLANATIONS OTHER SUGGESTED EXPLANATIONS FOR ST SEEM WANTING

1. There is considerable evidence against atavisms, reversions to ancestral dental formulae with more teeth.[1]
2. Documentation of tooth bud splitting, with or without to local trauma, is scanty at best, and fails to explain observed patterns.[1]
3. Environmental factors could explain population differences, but no patterns or indications of specific factors have been noted.
4. Population variations may play a role, as in a Spanish series[19] where mesiodentes were not the most common ST.
5. Single gene inheritance is doubtful. Although ST are common, familial cases are generally few (although this can occur in specific populations)[41] and findings of a single ST in two family members[1] may be coincidental, given general frequencies.
6. Hyperactivity of the dental lamina occurs in some situations,[9] but specific implications are wanting.
7. While a molecular etiology has been suggested, details are vague.[41] Certainly specific mutations cause ST, but no one gene is responsible,[2] and pathogenetic contributions, as with SHH, differ from a primary general cause.

These proposals treat ST as a single entity with a single explanation, and fail to explain localizations or to differentiate mesiodentes from other ST. There is sufficient evidence for causal heterogeneity to reject such approaches, and the factors suggested here explain a far wider range of observations than any of these alternatives.

QUESTIONS THE SUGGESTED MECHANISMS LEAVE SEVERAL QUESTIONS OPEN, INCLUDING

1. Do buckling effects on ST throughout the dentition suggest a role in normal initiation? This could involve localized areas of weakness related to normal structural or molecular inhomogeneities.
2. Do similar mechanical issues apply to hypodontia (although racial differences in commonest affected teeth45 suggest added levels of complexity here)?
3. Even though syndromic supernumeraries[2] show that Mendelian molecular processes can be involved, it is uncertain why non-syndromic familial multiples are so rare.
4. While mechanical effects on morphogenic fields similar to that suggested for intestinal crypts[23] are plausible, the

relationships of specific molecular genes and mutations to buckling need to be elucidated.

CONCLUSIONS

The most common ST are premaxillary, where unique causative factors include a midline vulnerability accentuated by broadening of the area, as with diastemata, and absent in the mandible. Multifactorial effects from genetic variants also contribute, while SHH signaling related to midface induction is of particular importance, and promotes palatal locations. It may affect ST morphology, with more complex tuberculates in the primary dentition, and simpler conicals in the secondary. There are also contributions from dental lamina buckling.

Growth differences in adherent layers of the lamina can also cause ST formation from buckling throughout the dentition. Mechanical factors control stress, with the greatest at the middle, least at the ends, and increases with greater lamina length. Effects are clearest with multiple (5 or more) ST, where premaxillary factors are minimized, and explain multiple ST predominance in the mandible, with mostly premolars, mostly upper jaw molars, and relatively few incisors. Contributions to normal tooth initiation are also possible.

Methodological and epidemiological issues affect assessments, and reports are often incomplete. Tooth groups need to be separated, numbers of patients with specific findings included, and details on individual teeth with multiples provided.

Although numbers are small, excess mesiodentes with familial ST suggest different pathogenetic processes with non-syndromic Mendelian forms.

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As the sole author, I contributed everything in the paper.

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