RESEARCH REVIEW

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Syndromes with Supernumerary Teeth

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While most supernumerary teeth are idiopathic, they can be associated with a number of Mendelian syndromes. However, this can also be a coincidental finding, since supernumerary teeth occur in 6% or more of the normal population. To better define this relationship, we analyzed the evidence for specific associations. We excluded conditions with a single affected patient reported, supernumerary teeth adjacent to clefts or other forms of alveolar disruption (as secondary rather than primary findings), and natal teeth, which can involve premature eruption of a normal tooth. Since, the cause of supernumerary teeth shows considerable heterogeneity, certain findings are less likely to be coincidental, such as five or more supernumerary teeth in a single patient, or locations outside of the premaxilla. We found only eight genetic syndromes with strong evidence for an association: cleidocranial dysplasia; familial adenomatous polyposis; trichorhinophalangeal syndrome, type I; Rubinstein–Taybi syndrome; Nance–Horan syndrome; Opitz BBB/G syndrome; oculofaciocardiodental syndrome; and autosomal dominant Robinow syndrome. There is also suggestive evidence of an association with two uncommon disorders, Kreiborg–Pakistani syndrome (craniosynostosis and dental anomalies), and insulin-resistant diabetes mellitus with acanthosisnigricans. An association of a Mendelian disorder with a low frequency manifestation of supernumerary teeth is difficult to exclude without large numbers, but several commonly cited syndromes lacked evidence for clear association, including Hallermann–Streiff syndrome, Fabry disease, Ehlers–Danlos syndrome, Apert and Crouzon syndromes, Zimmermann–Laband syndrome, and Ellis–van Creveld syndrome. © 2016 Wiley Periodicals, Inc.

Key words: dental anomalies; extra teeth; supernumerary teeth and syndromes; syndromes with extra teeth

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INTRODUCTION

Supernumerary teeth (ST) represent one of the most common human malformations. With methodological issues as well as population differences, figures vary, but their prevalence may reach 6%, or possibly even higher [Anthonappa et al., 2013a]. This anomaly is etiologically heterogeneous and is highly variable, differing in numbers, location, morphology, relationship to other teeth, presence in the primary and/or permanent dentition, and associated problems, such as impaction, as well as other issues [Mallineni et al., 2014].

Most ST are idiopathic, but they also occur in genetic syndromes, where they can be an important diagnostic clue [Wijn et al., 2007], and provide insights into basic developmental pathways and processes [Kantaputra et al., 2008]. Unfortunately, there is a great deal of confusion over the nature of this association, and considerable variation in the criteria used for validation. To better define this relationship, we analyzed evidence for specific associations, and found only eight genetic syndromes where a significant connection could be supported, plus two where it was suggestive.

The syndromes reviewed were clinically defined disorders that included non-dental findings, and that are related to presumed or documented abnormalities of a single gene. Chromosomal abnormalities, including deletions of multiple genes, were excluded. ST are defined as additional teeth beyond the

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normal dental components. They are associated with facial clefts, probably as a non-specific secondary consequence of disruption [Garvey et al., 1999] and conditions with alveolar disturbances, as with clefts,and orofaciodigital syndrome I (OMIM 311200) were not included. Natal teeth were also excluded, since they can involve premature eruption of a normal tooth, rather than an additional one, as with Hallermann–Streiff syndrome [Ahn and Kim, 2006] and seem to represent a separate pathogenetic process, since they are typically not found with other types of ST, and are rare in the general syndromes.

We used a Pubmed search for "supernumerary teeth" and syndrome through 2015 for a preliminary assessment, followed by a further review of individual disorders. Disorders were excluded if only a single affected patient had been reported. Commonly cited examples of this include fucosidosis [Macpherson, 1991], incontinentiapigmenti [Himelhoch et al., 1987], Marfan syndrome [Mallineni et al., 2012], mucopolysaccharidosis type VI [Kayserili and Kantaputra, 2012], and enamel-renal-gingival syndrome [Kantaputra et al., 2014].

One difficulty in assessing possible associations of rare syndromes with ST is the background frequency of ST, which may be 6% or higher [Anthonappa et al., 2013a], making coincidence likely if only a few occurrences have been reported. However, the finding of ST shows considerable heterogeneity, and certain findings are less likely to be the result of coincidence. Unfortunately, the epidemiologic data on idiopathic ST varies considerably among studies, and there are considerable methodological issues as well as population differences [Anthonappa et al., 2013b].

Despite this, some characteristics of idiopathic ST can be taken as generally valid. First, most idiopathic ST manifest as a single tooth. While figures vary [Ata-Ali et al., 2014; Bereket et al., 2015], this applies to about 80%, while 15–20% show two, 3–4% three, and only 1% or so more. For five or more, which we will refer to as multiples, Açikgöz et al. [2006] found a frequency of 0.06%. Second, the locations are far from random. Probably 80–90% of patients with ST have maxillary findings, primarily anterior, with about half of these as mesiodens between the central incisors. On the other hand, involvement of the mandibular incisors is exceptional [Rajab and Hamdan, 2002]. As a result, certain types of ST are less likely to be coincidental when associated with a specific condition, although this is still possible. One additional consideration is the frequency of the association with a specific syndrome. If this is low, it may be difficult to appreciate without a specific survey of a large number of affected patients.

Finally, there is the possibility of a syndrome and a genetic form of ST coincidentally segregating together. Although the literature often states that familial reports are common, one review [Anthonappa et al., 2013a] found only 24 kindreds, the majority with just two members, each with a single mesiodens (plural = mesiodentes), probably the most common form. Therefore, it would seem that three or more members with both a syndrome, and ST together, especially multiples, are unlikely to be coincidental, although this may still not represent a true association. Brief clinical and gene descriptions are taken from OMIM, unless otherwise stated.

SUPERNUMERARY TOOTH-ASSOCIATED SYNDROMES

The two most commonly cited syndromes are cleidocranial dysplasia and familial adenomatous polyposis (FAP). Cleidocranial dysplasia (CCD; OMIM 119600) is a well-known autosomal dominant condition, where the most obvious findings are persistent open skull sutures, underdevelopment of the clavicles, and dental abnormalities. It is caused by loss-of-function of the *RUNX2* gene (OMIM 600211), which encodes a transcription factor, CBFA1 [Otto et al., 2002].

ST are common and, in fact, the rule: In one study, 18 of 19 patients had ST, with frequency in different areas from 22% in the maxillary incisor region to 5% in the molar regions. This was limited to the permanent teeth, most likely related to reactivation of the dental lamina after normal dental crown development. The ST can be single or multiple, and in a few patients, literally dozens can occur [Jensen and Kreiborg, 1990]. With a majority of patients showing ST, usually as multiples, this is the most prominent syndrome association.

Familial adenomatous polyposis (FAP; OMIM 175100) was originally distinguished from Gardner syndrome by the absence of extra-colonic findings, especially oral, and maxillofacial abnormalities, but this is now considered a single autosomal dominant condition with highly variable expressivity. It is characterized by the development of 100–1,000 of adenomatous polyps of the colon and rectum, which can become cancerous. It is caused by haploinsufficiency of *APC* (OMIM 611731), a tumor suppressor gene. ST appeared in 11–27% of patients, mostly between teeth in the alveolar bone or attached to follicle of an impacted tooth. Common sites were anterior and around canines [Wijn et al., 2007]. Although less common, six other syndromes also have multiple reports of affected patients and kindreds that support an association with ST.

Nance–Horan syndrome (NHS; OMIM 302350) is X-linked, with congenital cataracts, dental abnormalities, dysmorphic features, and occasional intellectual disability [Burdon et al., 2003]. ST are common in the central maxillary area, including mesiodentes. Males tend to be more severely affected. It is caused by mutations in NHS (OMIM 302350), which regulates actin remodeling and cell morphology. In males there are reports including two patients with mesiodens [Nance et al., 1974], one spade-shaped mesiodens, two with maxillary incisors, one "abnormal shape" [Sharma et al., 2008], "tooth in the anterior mandible" [Hennekam et al., 2010a] "abnormally shaped teeth" [Reches et al., 2007], incisors [Coccia et al., 2009, family D], and by report: "teeth removed from the upper jaw in infancy," with another patient with "crowded teeth" (not specified as supernumerary) [Nance et al., 1974]. In females, there are three patients with mesiodens in primary dentition [Walpole et al., 1990], three lateral incisors plus third molars absent [Hibbert, 2005], and multiple extracted ST [Coccia et al., 2009, family D]. Also, central incisors have been involved [Bixler et al., 1984] . Here, the ST seem similar to those seen in idiopathic cases, that is, the anterior maxilla is involved with one or two ST. However, the frequency is certainly increased beyond what might be expected by chance. Interestingly, two of the females with ST appeared to have had more severe findings than males.

Trichorhinophalangeal syndrome, type I (TRPS1; OMIM 190350) is an autosomal dominant disorder that includes skeletal anomalies with cone-shaped phalangeal epiphyses, and a characteristic facies with sparse scalp hair, bulbous tip of the nose, long flat philtrum, thin upper vermilion, and protruding ears [Maas et al., 2015]. It is caused by mutations in zinc finger transcription factor *TRPS1* (OMIM 604386).

Eleven affected patients from 10 families have been reported with ST. All patients with multiple ST involved both the maxilla and mandible, but the incisors were not always involved. However, for five patients with single ST, four were incisors [Hobolth and Mune, 1963; Giedion, 1966; Kuna et al., 1978; Paterson and Thomas, 2000], and one had a supernumerary mandibular premolar [Rosenbaum et al., 1978; patient 3]. Multiples ranged from five in the premolar, and molar areas of the maxilla and mandible with premolar morphology [Kantaputra et al., 2008] to 18 in the premolar, and molar regions of the maxilla and mandible [Kunotai et al., 2016; patient 2; submitted], with the latter also missing the right first maxillary and mandibular premolars. Patient 1 of Kunotai et al. [2016] had seven ST in the maxilla and eight in the mandible. Karacay et al. [2007] reported a patient with three ST by the lower second premolars, one on the right, and two on the left. Patient 1 of Rosenbaum et al. [1978] had eight anterior maxilla ST, and two mandibular premolars, and patient 2 an unspecified number in the posterior maxilla and mandible. An estimated 100 patients with TRPS type I have been reported by mid 2015 [Orphanet, 2015]. For TRPS type I, the presence of 11 patients with ST seems significant. We are convinced that patients with TRPS1 with ST are under-reported, since most of the ST areunerupted and impossible to detect without panoramic X-ray examination. Additionally, many were multiples involving both the maxilla and mandible, and three patients had eight or more. These atypical idiopathic findings suggest a distinct pathogenesis, rather than a coincidence.

Opitz BBB/G syndrome (GBBB1; OMIM 300000) involves midline findings of widely spaced eyes, hypospadias, cleft lip/palate, laryngotracheoesophageal anomalies, imperforate anus, developmental delay, and cardiac defects. An X-linked form is caused by mutations in *MIDLINE 1*; *MID1* (OMIM 300552), but this accounts for only a minority of patients, and autosomal forms exist that are difficult to distinguish clinically [So et al., 2005].

da Silva Dalben et al. [2008] examined dental abnormalities in 21 clinically diagnosed males, all with some form of cleft lip and palate. In the mandible, which was intact, 11 had a supernumerary anterior incisiform tooth of the mandible, two had additional supernumerary right and left maxillary incisors, and another had three supernumerary left maxillary left premolar maxillary teeth. While the maxillary teeth may have been related to the clefts, the supernumerary mandibular tooth in over half of these patients is clearly separate. In this condition, ST are present in almost half of all patients, and the incisiform mandibular teeth are unusual otherwise. However, their location makes pathogenetic sense in terms of the other midline abnormalities seen in this condition.

Rubinstein–Taybi syndrome (RSTS1: OMIM 180849; RSTS2: OMIM 613684) is genetically heterogeneous, with mutations affecting *CREBBP* (OMIM 600140) in about 50% of patients or *EP300* (OMIM *602700) in 3–8%. Findings include intellectual disability, short stature, microcephaly, broad thumbs and halluces, and a distinctive facies, among other findings. ST were noted in 15% of patients in one series, and previous patients had been noted in the literature [Hennekam and Van Doorne, 1990].

Oculofaciocardiodental syndrome (OFCD or MOCPS2; OMIM 300166) is an X-linked dominant disorder that is lethal in males. Eye anomalies include congenital cataract and microphthalmia, and there is a typical facial appearance, with structural cardiac and dental abnormalities. It is caused by mutations of the BCL6 Corepressor; *BCOR* (OMIM 300485) [Hilton et al., 2009].

Hilton et al. [2009] found *BCOR* mutations in three patients from two affected kindreds, and both duplicated teeth and hypodontia, but without detail. Patient 3 of Schulze et al. [1999] appeared to have "duplicated permanent canines and hypodontia of the right lateral incisor." This would be of particular interest because supernumerary cuspid canine is a rarely seen condition. There are enough reports of ST in the relatively small number of patients with this condition to support a true association, and the unusual involvement of the canines lends further credence.

Robinow syndrome, a skeletal dysplasia with short stature secondary to mesomelic limb shortening, an appearance reminiscent of a fetal face, and renal, vertebral and male genital anomalies, can be both autosomal dominant or recessive, but ST appear to be associated with only the dominant form (DRS1: OMIM 180700). A minority of families have hypomorphic alleles of wingless-type MMTV integration site family, member 5A; *WNT5A* (OMIM 164975). Mazzeu et al. [2007] evaluated 38 affected individuals, and reviewed 50 from the literature, 37 classified as recessive, and 51 as dominant. There were four patients with ST in the dominant group, and none in the recessive [Mazzeu et al., 2007].

Finally, two rare syndromes have had ST reported in several members of a single kindred. We consider these to be likely associations, but more data are needed before this can be confirmed.

Nieminen et al. [2011] found mutations in *IL11RA* (interleukin 11 receptor, alpha; OMIM 600393) in patients in five families with a Kreiborg–Pakistani syndrome (CRSDA; OMIM 614188) which includes craniosynostosis, delayed tooth eruption, and ST. Keupp et al. [2013] identified patients from six families with a Crouzon syndrome-like appearance and mutations in the same gene. Four members of one of the families of Nieminen et al. [2011], had one to seven ST about 4 years after eruption of the permanent dentition.

Rüdiger et al. [1983] reported three siblings with insulin-resistant diabetes mellitus with acanthosisnigricans (OMIM 610549), bitemporal narrowing of the skull, body fat paucity, enlarged ears, nose, chin, and finger tips, short fingers, protrusion of the globes- and dental anomalies (ST, severe and premature caries, abnormally prominent lower canines, and upper incisors). We are not aware of other families with this condition. The insulin resistance was heterogeneous, but other patients did not apparently have ST, save for a Japanese woman with four ST, and a distinct physical phenotype [Nakashima et al., 1992].

EXCLUSIONS OF COMMONLY CITED SYNDROMES

We do not think that disorders with a single patient with ST generally need to be considered in detail (see above). While there may have been subsequent reports that we have missed, a significant number of additional affected patients that would lead to inclusion seems unlikely. However, it is worth justifying the exclusion of certain other conditions with a suggested association.

Hallermann–Streiff syndrome (HSS; OMIM 234100) may include premature eruption of teeth before or shortly after birth, which are often misdiagnosed as ST [Ahn and Kim, 2006].

The association of Fabry disease with ST is based on two reports [Regattieri and Parker, 1973; Brindley et al., 1975], but this was not seen in 13 patients surveyed for oral and craniofacial findings [Baccaglini et al., 2001], or to our knowledge in more recent reports. Also, in the α-galactosidase A deficient ($Aga^{-/-}$) mouse model of Fabry disease, the teeth showed no gross morphological abnormalities, and ST were not noted [Goldberg et al., 2005]. This seems to be pathogenetically distinct from other conditions with ST, and we found only two other associations with storage disorders, both single occurrences: mucopolysaccharidosis type VI [Kayserili and Kantaputra, 2012], and fucosidosis [Macpherson, 1991]. We conclude that these co-occurrences are coincidental.

There are several types of Ehlers–Danlos syndrome characterized by hyperextensible skin secondary to a variety of collagen defects. This is a relatively common condition, with an estimated European prevalence of 5/100,000 for the classic type (OMIM 130000), and 12.5 for hypermobility (OMIM 30020) [Orphanet, 2015]. Five patients with ST in four families have been reported: (i) Odontogenickeratocyst and multiple ST in one patient [Ferreira et al., 2008]; (ii) Father with one maxillary premolar and son with eight unerupted ST [Melamed et al., 1994]; (iii) A child with ST [Majorana and Facchetti,1992]; and (iv) One patient with four maxillary, and one mandibular ST removed with 14 affected family members without ST [Premalatha et al., 2010]. The patients tend to have five or more ST, which is suspicious for an association, but, considering the frequency of this disorder, the number of patients does not seem excessive.

As discussed above, there may be a connection between ST and the Kreiborg–Pakistani syndrome of craniosynostosis and dental anomalies, and Apert and Crouzon syndromes have also been cited. However, for the last two, the actual number of documented patients is low, as is the number of teeth per patient. Of nine patients in a study of Apert syndrome with panoramic radiographs, two had a single ST in the anterior maxillary area [DalbenGda et al., 2006]. There was also negative evidence, for example, Stavropoulos et al. [2011] evaluated serial panoramic radiographs for 26 patients with Crouzon syndrome, and 23 with Apert syndrome. While he extensively evaluated tooth agenesis, ST were not mentioned. We suspect that any increased rates of ST in these syndromes are small, and that most probably they are particularly likely to be noticed with common radiologic investigations, a small oral cavity, and agenesis of other teeth.

At least seven patients have been reported as having Ellis–van Creveld syndrome with ST [Cahuana et al., 2004; Hennekam et al., 2010b]. These tended to be single and in the mandible. However, this may be associated with the disruption from the characteristic notching of the lower alveolar process, and therefore, an occasional secondary manifestation.

We tentatively rejected the association of Zimmermann–Laband syndrome (ZLS1; 135500 and ZLS2; 616455) with ST. This is a disorder that includes gingival fibromatosis, small distal phalanges and nails, hepatosplenomegaly, and hirsutism, which can overlap with other conditions with gingival fibromatosis [Haytac et al., 2007]. It is genetically heterogeneous: Kortüm et al. [2015] found *KCNH1* or *ATP6V1B2* mutations in eight of 24 patients. Castori et al. [2013] reviewed 52 patients. Of these, three had ST [Chadwick et al., 1994; Holzhausen et al., 2003; Chacon-Camacho et al., 2011], ranging from one to five in number. We conclude that this is probably a chance finding in a condition where gingival-related issues make dental radiographs, and the consequent ascertainment of coincidental ST more likely.

DISCUSSION

Whether or not, a specific finding and a specific syndrome are connected is not always obvious. For ST, a high background frequency makes coincidence a particular problem, while at the same time making small increases in frequencies with specific syndromes difficult to distinguish from chance occurrences.

This is further complicated by ascertainment and publication biases, especially since ST may be missed without a panoramic X-ray examination. We suspect that this is the explanation for suggested associations with Apert and Crouzon syndromes, where other issues increase the likelihood of a comprehensive dental examination, but case series seem to show only occasional examples of ST at best.

Overall, associations of ST with specific syndromes need to be assessed with caution, and several commonly cited conditions failed to meet basic criteria. In particular, while may they raise suspicions, as with Fabry disease and Ehlers–Danlos syndrome, a few examples are insufficient proof with more common disorders.

For rarer conditions, more than one kindred should ideally show the association. However, in two disorders, Kreiborg–Pakistani syndrome, and insulin-resistant diabetes mellitus with acanthosisnigricans, this held for only one family. Still, with four concordant members in one kindred and three in the other, and no evidence of independent segregation of the syndrome or the ST, coincidence seems unlikely, especially with multiple ST involved. For the Kreiborg–Pakistani syndrome, the association was not seen in other patients with the syndrome with the same mutation, which argues against a simple genotype–phenotype correlation, and other modifying genes may be involved.

With these two conditions, additional patient reports are needed to confirm or refute the relationship. Even with a limited number of validated syndromes, clinical heterogeneity suggests likely pathogenetic differences. For example, patients with Nance–Horan syndrome usually have one or two ST in the anterior maxilla, and mesiodentes are common, while patients with TRPS1 can have multiple ST throughout the jaw, and mesiodentes are rare.

One unanswered question is the possibility of sex biases in the autosomal syndromes. With non-syndromal, idiopathic ST, there is a distinct male predilection, but a major sex difference seems

unlikely with syndromic occurrences, but there does not seem to be good data ruling some degree of bias in or out.

It is remarkable that, despite the frequency of ST in the general population, relatively few genetic syndromes appear to show good evidence of ST as a primary component. Distinct clinical pictures may represent heterogeneous pathogenetic mechanisms in some syndromes, as well as a differences from the more common idiopathic types. With this, we would plead for more complete clinical descriptions of ST. We would also discourage the practice of citing conditions as having ST based on minimal observations.

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