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ORIGINAL ARTICLE

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# Oral features in Apert syndrome: a histological investigation

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**Structured Abstract**

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***Objectives –*** The number of publications on the oral features in Apert syndrome is limited. The present study investigated dental tissues in Apert syndrome histologically, to determine the nature and extent of anomalies, to provide some insight into the nature of the condition, and to explain how observed anomalies may affect the dental management of individuals with Apert syndrome.

***Setting and Sample Population –*** Extracted primary and secondary teeth were collected from patients with Apert who had attended the Australian Craniofacial Unit, Adelaide, South Australia. The total study sample comprised 13 individuals, aged from 14 to 21 , with nine men and four women.

***Material and Methods –*** A total of 40 teeth were available for histological examination (the number belonging to each individual varied from 2 to 5 per patient). The teeth were sectioned longitudinally, and one-half of each tooth underwent decalcification. Sections were stained with H&E for routine histological examination. Ground sections were prepared from undecalcified tooth halves.

***Results –*** Histological assessment of the dental hard tissues revealed an intact enamel and dentinal structure but some irregularities were noted in the region of the dentino-enamel junction (DEJ), which could affect caries progression and also make dental management more difficult.

***Conclusion –*** This study identified histological anomalies of the DEJ of Apert syndrome teeth. An improved appreciation of the nature and extent of dental anomalies in Apert syndrome should assist clinicians when undertaking management of affected individuals.

**Key words:** Acrocephalosyndactylia; craniosynostoses; dentino-enamel junction; dentistry; tooth

## Introduction

Apert syndrome is an autosomal dominant disorder that was first described by Wheaton in 1894 (1). Subsequently, it was given its eponymous name after being described by Apert in 1906 (2). It is a form of craniosynostosis, a condition in which there is pre-mature closure of certain calvarial sutures. The coronal suture is specifically affected in Apert syndrome, leading to characteristic head shapes secondary to restriction of growth perpendicular to the suture and compensatory growth in

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the remaining sutures. This produces a wide midline defect affecting the area of the metopic and sagittal sutures. Apert syndrome is an example of a syndromic craniosynostosis, where an underlying genetic mutation has been identified, and multiple sutures are affected along with other manifestations.

The prevalence of Apert syndrome has been reported as 1:200 000, constituting a small proportion of all cases of craniosynostosis, and it occurs equally in men and women in population-based studies, but clinical studies have revealed more affected women (3). Despite its rarity, Apert syndrome has been studied by more authors than any of the other three craniosynostosis syndromes. The triad of features that is associated with Apert syndrome includes craniosynostosis, turribrachycephaly and midface hypoplasia (4). Gorlin (5) described the head as being broad, with the metopic and sagittal sutures widely patent during infancy, resulting in turribrachycephaly (towering skull). The characteristic craniofacial features of Apert syndrome are shown in Fig. 1. Common findings include maxillary hypoplasia, which results in shallow orbits and proptosis, hypertelorism and down-slanting palpebral fissures, along with syndactyly of the hands and feet (4). There have been reports of affected individuals having anomalies of the viscera, elbows and shoulders, skeleton and central nervous system, and this often results in impaired mental function, emphasizing the need for ongoing care by a wide range of medical and surgical specialists.

The clinical and genetic factors associated with Apert syndrome have been studied extensively. The majority of studies have focused on the frequency and resulting effects of the two major types of mutations affecting the FGFR2 gene. Park et al. (6) summarized the genetic and environmental interactions in Apert syndrome. The mutations in the resulting FGFR2 gene alter the three-dimensional shape of the receptor and affect its role in growth and development, resulting in pre-mature fusion of bones in the skull, hands and feet of the patient with Apert. During craniofacial development, FGF signalling is involved not only in craniofacial bone formation, but also in the formation of the palate, salivary glands, teeth, craniofacial muscles and tongue muscles (7). It has been well documented that FGFR2 also plays an important role in tooth development. For example, it has been shown that in mice with FGFR2 mutations, tooth development fails to develop beyond the bud stage, with defects in the salivary glands and palate also being recorded (7). Therefore, it seems feasible that FGFR signalling mutations influencing the craniofacial features in Apert syndrome might also influence the dental tissues, leading to alterations in size and shape of the teeth. Furthermore, FGF signalling plays an important role in the epithelial–mesenchymal tissue interactions that occur normally between the inner enamel epithelium and the dental papilla during odontogenesis, and altered expression of this growth factor at critical stages of development in Apert syndrome could lead to a range of effects on the dentition.

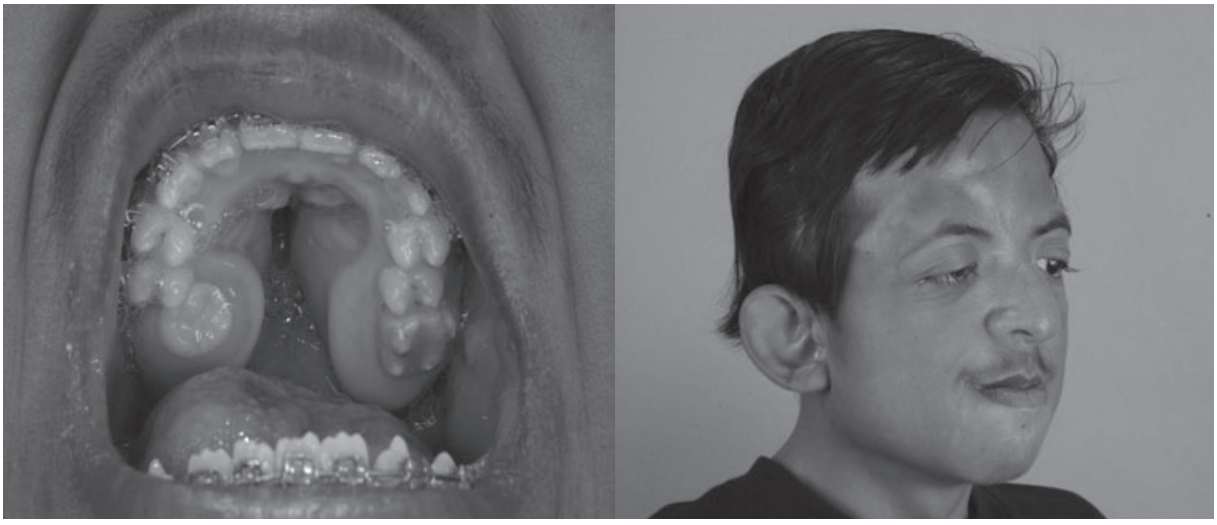

*Fig. 1.* Intra- and extra-oral photographs of a male with Apert syndrome.

Craniofacial features of Apert syndrome will always be an area of focus in the literature, as developments made can help to improve function, appearance and ultimately the long-term survival of the patient with Apert. With advances in medical imaging, such as 3D-CT scanning and in-utero imaging, greater details of the craniofacial skeleton can be obtained. The oral and dental manifestations of the syndrome have been described in only a few studies that have focused on macroscopic features of the syndrome (8, 9). Various studies have recently identified similar intraoral characteristics, including a crossbow or trapezoid-like mouth shape with often protruding lips, a hypoplastic maxilla that appears retruded and thus a Class III malocclusion with an edge-to-edge incisor relationship and anterior open bite (10–12). Delayed tooth eruption times of almost a year have also been reported. Specific dental anomalies were reported by Dalben et al. (12), including enamel projections, long canine cusps, supernumerary teeth, dental fusion, enamel opacity, enamel hypoplasia, tooth agenesis, ectopic tooth positioning and tooth impaction.

Common trends have emerged from previous studies of Apert syndrome, with anomalies in growth of the calvaria and facial skeleton being an important area for investigation. Considerable numbers of patients have been studied across a range of ethnicities, involving children of different ages. This provides a valuable clinical spectrum of the variation seen in the craniofacial region and the common skeletal defects of Apert syndrome. However, Apert syndrome is a rare disorder, and consequently sample sizes reported in previous individual studies have been small. Therefore, limited data are available for quantitative comparisons with findings often based on single case presentations that authors have attempted to associate with the entire spectrum of Apert syndrome. Generalization of typical features associated with Apert syndrome can be made to some extent, but each individual has a unique presentation that needs to be taken into account when management strategies are developed.

Apart from a study by Solomon et al. (13) on mucopolysaccharides in the palatal mucosa of patients with Apert , information on the histological appearance of the oral tissues in Apert syndrome is scarce. This study aims to provide more definitive insights into the histological structure of the dental tissues in Apert syndrome. The knowledge gained from this study should alert dental practitioners to the challenges that may arise when managing oral problems in patients with Apert syndrome.

## Materials and methods

### Sample population

This study involved 13 patients with Apert syndrome for whom records are kept in the Australian Craniofacial Unit (ACFU) at the Women's and Children's Hospital, Adelaide, South Australia. Craniosynostosis syndromes, including Apert syndrome, are a major area of focus in both surgical and multidisciplinary management by the ACFU, and thus a relatively high number of patients have been treated with this condition despite its rare nature. Ethics approval was obtained from the Ethics Committee at the WCH (WCH200A).

### Extracted teeth for histological study

Teeth of patients diagnosed with Apert syndrome that had been extracted previously following ACFU surgical procedures in association with each patients particular management protocol formed the study sample for histological analysis. Forty teeth stored in formalin were evaluated for study, including both primary and secondary dentitions.

Each tooth was bisected longitudinally. One-half of each tooth underwent decalcification and was processed for routine histological examination. Five micron sections were stained with haematoxylin and eosin (H&E). Ground sections were prepared from the remaining undecalcified tooth halves enabling examination of both the enamel and dentine. All specimens were examined using an Olympus BH2 microscope and photographed using an Olympus Altra 20 digital camera (Olympus Australia, Mt. Waverley, Victoria, Australia).

The images provided in this article represent only a small proportion of the samples prepared and examined. It should be noted that, to avoid sampling bias, all areas of tooth structure visible in histological analysis were assessed and noted with features being consistently described. Images that were chosen for inclusion as figures provided the best representations of the features under study.

## Results

Examination of the dental hard tissues of extracted teeth from Apert syndrome individuals revealed no gross anomalies in enamel or dentinal structure. Figures 2 and 3 show the relatively normal dentinal appearance of an patient with Apert syndrome. The enamel also appears normal despite the difficulties in imaging because of optical light interference.

When the dentine and enamel were examined at higher magnification, the DEJ appeared to show some inconsistencies within its structure. The literature is clear in describing the DEJ as normally being scalloped in appearance in ground sections and showing marked scalloping in demineralized sections (14). However, all of the specimens examined failed to show this feature. Histological sections showed either a flat DEJ or a wavy, inconsistent junction that did not conform with the structure usually described (Fig. 4).

Other structures seen in the enamel included enamel tufts and lamellae, which are developmental features relating to the formation of the enamel and dentine whose structure is influenced by the DEJ formation. Four specimens, or 10% of the teeth cut in a mesio-distal plane showed irregularities including small dark projections from the dentine into the enamel. Some areas appeared with no projections and some tufts/lamellae were present (Fig. 5). There was also evidence of a broken DEJ in a few Apert syndrome specimens, with the large gaps appearing to be artifacts that had occurred during preparation (Fig. 6).

*Fig. 2.* Ground section of an Apert syndrome tooth (×10 magnification). Note the characteristic curvature of the dentinal tubules approaching the dentino-enamel junction (see arrows).

*Fig. 3.* Ground section of an Apert syndrome tooth (×40 magnification). Note the defined tubular structure of the dentine (see arrows).

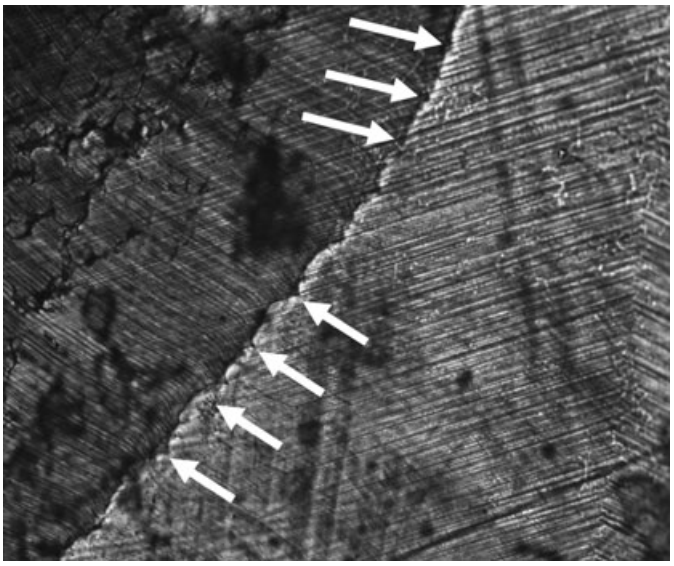

*Fig. 4.* ×10 microscopic view of a ground section showing inconsistent structure at the dentino-enamel junction. Scalloping is non-existent towards the top of the image (top arrows) and is marked towards the bottom of the image (bottom arrows).

H&E stained sections revealed a relatively intact dentinal structure. The tubular structure appeared to be normal and did not show any obvious irregularities when examined histologically. However, the DEJ again revealed variation. It showed a profile that differed from descriptions in the literature. Scalloping was rarely seen in the Apert specimens and, if present,

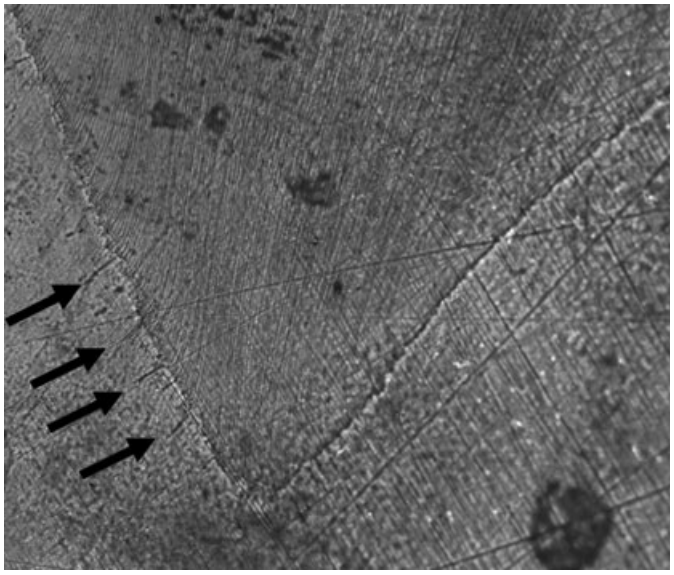

*Fig. 5.* ×20 microscopic view of a ground section showing some evidence of projections or lamellae into the enamel from the dentino-enamel junction. This is more marked on the left of the image (see arrows).

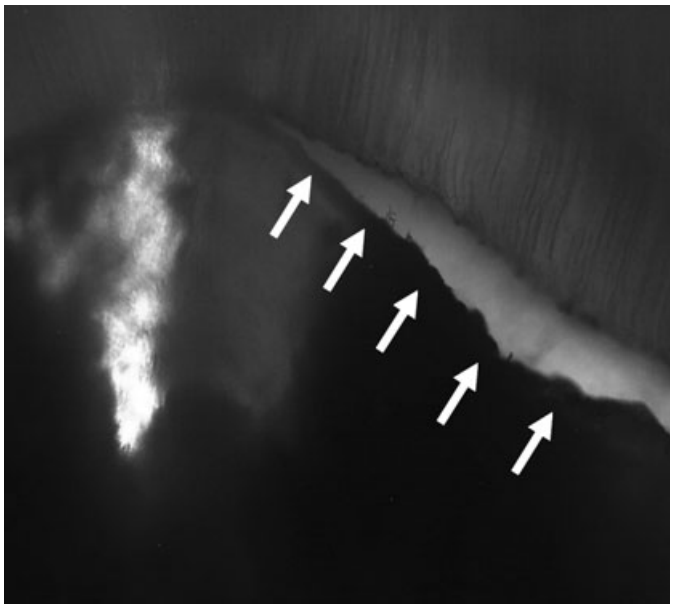

*Fig. 6.* ×10 microscopic view of a ground section showing marked spacing between the enamel and dentine structures at the dentino-enamel junction, identifying a defect in section preparation (see arrows).

showed an inconsistent or irregular pattern (Figs 7 and 8).

## Discussion

Despite considerable documentation on the general features of Apert syndrome, there is little published literature on the oral effects of the syndrome. This study has provided some new insights into the histological features of the dental tissues in Apert syndrome. Given the rarity of the condition, a relatively large sample of Apert teeth was available for study.

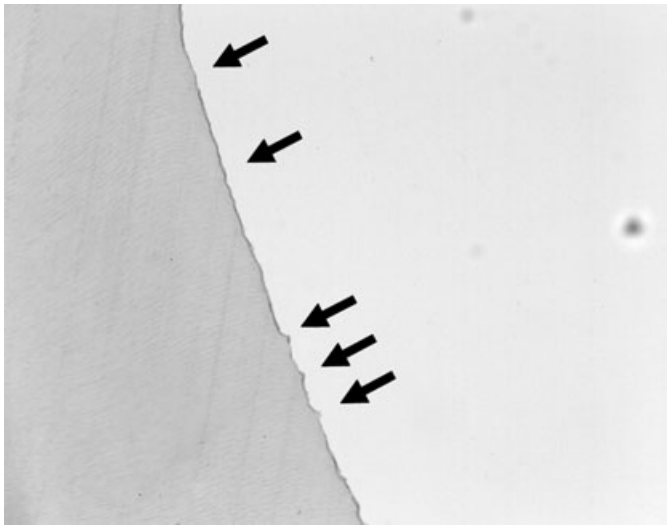

*Fig. 7.* ×10 microscopic view of the dentine (darker area) and dentino-enamel junction (DEJ) (see arrows), which shows a flattened DEJ with some irregular scalloping. The lighter area identifies the demineralized enamel space.

An early description of the DEJ was given by Tomes (15), who implied that all enamel is festooned (showing a looped or curved appearance) towards the dentinal surface. Few studies have questioned this concept, although Rywkind (16) noted that in some teeth the scalloping is irregular in size and distribution and sometimes absent. Gustafson (17) confirmed the basic arcade-shaped appearance of the junction, but agreed that the development of the scallops varied from tooth to tooth, and suggested that the pattern may be characteristic of the individual. The authors noted that the arcades were more pronounced in fluorosed teeth. Falin (18) described the DEJ in Bronze Age teeth as being flat or slightly festooned in pre-molars and molars, and scalloped in canines and incisors. No comparable study appears to have been carried out in teeth of modern origin. Scott and Symons (19) commented upon the variation in size of the dome-shaped scallops, which are usually most marked in the cuspal region, but are occasionally absent. The location of the most marked scalloping, as described by Schour (20), was in the gingival third of teeth. Whittaker et al. (21) found tufts and lamellae commonly within specimens of normal tooth structure but, in our

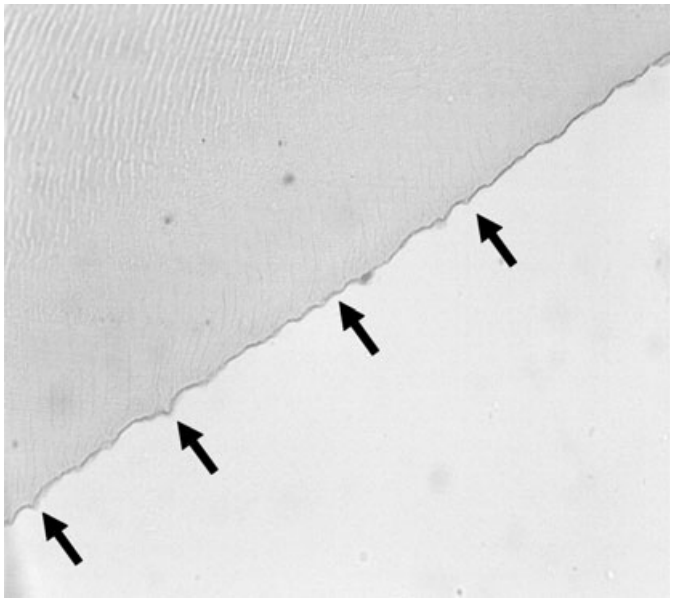

*Fig. 8.* Molar cervical region of an Apert syndrome tooth that has been H&E prepared. Note the irregular scalloping along the entire length of the dentino-enamel junction. The arrows show some of the more pronounced irregularities.

study, tufts and/or lamellae were rarely visible (only appearing in 10% of samples). This may suggest anomalies associated with DEJ development. In our study, scalloping was absent or irregular in all areas of the crown and seemed consistently absent in the cuspal regions, where it has previously been described as being profound. The preparation of the samples caused some trauma to specimens, especially during the hand polishing stages, and this may have contributed to the artifacts seen.

Given that FGF signalling (particularly FGFR2) plays an important role in the formation of the teeth, and formation of the enamel and dentine is dependent on reciprocal epithelial and mesenchymal interactions, anomalies in FGFR signalling in Apert syndrome may affect dental development, leading to macroscopic and histological anomalies (22, 23).

So what do these findings mean for patients with Apert syndrome ? They suggest that changes should be considered to optimize the management of children with Apert syndrome, both dentally and orthodontically. Anomalies in the teeth of patients may predispose them to difficulties in tooth eruption, in maintaining good oral hygiene and in ensuring correct bonding of orthodontic brackets and placement of orthodontic wires. Hohoff et al. (10) reported on the difficulties associated with orthodontic treatment because of partially erupted teeth and soft tissue anomalies but Apert teeth may also be pre-disposed to poor bonding in restorative treatment and orthodontic bracket application. Histological anomalies of the enamel and dentine interface may also promote the advance of caries in patients teeth. Interestingly, Mustafa et al. (24) assessed caries levels in craniosynostosis syndromes and non-craniosynostosis groups, with results showing a significantly greater caries prevalence in individuals affected by Apert syndrome. Further focus on caries prevalence in future studies should provide more conclusive data. Dalben et al. (12) reported on the oral health status of children with syndromic craniosynostosis, including 10 patients with Apert syndrome, and showed a predominance of caries (measured by DMFT (Decayed, missing, filled teeth) scores) in these patients, concluding that there is an increased need for follow-up programmes by their dental practitioners. Anomalies in the DEJ interface may also affect the ability of materials to bond to the enamel and dentine, thus increasing the likelihood of de-bonding of materials while also increasing the risk of secondary caries. Further studies of the caries experience of patients with Apert would be valuable in ensuring that this risk is reduced and that appropriate management plans are implemented.

Overall, the findings of the present investigation indicate that there are anomalies in the oral hard tissues in patients with Apert syndrome. Further studies comparing the histological characteristics of teeth obtained from individuals with Apert syndrome with teeth obtained from unaffected individuals would further strengthen the findings. Although the study sample was limited in size because of the rarity of the syndrome, results showed that the dental tissues vary from normal histologically, and these variations have implications for the management of individuals with Apert syndrome.

## Clinical relevance

Children with Apert syndrome have obvious dysmorphic facial growth, particularly affecting the midface. The need for corrective surgery, therefore, is inevitable. The orthodontist faces challenges because of anomalies in the morphology of the teeth, crowding and delayed eruption. This study identified histological anomalies in

the dentino-enamel junction (DEJ) and an appreciation of the effects of these anomalies will assist clinicians in managing patients with Apert syndrome. Effective clinical management requires a close co-operation between the pedodontist, orthodontist and surgeon. Understanding the roles of each practitioner will ensure successful planning and delivery of treatment and result in optimal treatment outcomes for patients.

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