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Craniofacial and Dental Development in Costello Syndrome

Alice F. Goodwin,[1] Snehlata Oberoi,[1] Maya Landan,[1] Cyril Charles,[1] Jessica C. Massie,[1] Cecilia Fairley,[1] Katherine A. Rauen,[2] and Ophir D. Klein[1,2]***

[1]Program in Craniofacial and Mesenchymal Biology, and Division of Craniofacial Anomalies, Department of Orofacial Sciences, University of California San Francisco, San Francisco, California

[2]Department of Pediatrics, Institute for Human Genetics, University of California San Francisco, San Francisco, California

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Costello syndrome (CS) is a RASopathy characterized by a wide range of cardiac, musculoskeletal, dermatological, and developmental abnormalities. The RASopathies are defined as a group of syndromes caused by activated Ras/mitogen-activated protein kinase (MAPK) signaling. Specifically, CS is caused by activating mutations in *HRAS*. Although receptor tyrosine kinase (RTK) signaling, which is upstream of Ras/MAPK, is known to play a critical role in craniofacial and dental development, the craniofacial and dental features of CS have not been systematically defined in a large group of individuals. In order to address this gap in our understanding and fully characterize the CS phenotype, we evaluated the craniofacial and dental phenotype in a large cohort (n = 41) of CS individuals. We confirmed that the craniofacial features common in CS include macrocephaly, bitemporal narrowing, convex facial profile, full cheeks, and large mouth. Additionally, CS patients have a characteristic dental phenotype that includes malocclusion with anterior open bite and posterior crossbite, enamel hypo-mineralization, delayed tooth development and eruption, gingival hyperplasia, thickening of the alveolar ridge, and high palate. Comparison of the craniofacial and dental phenotype in CS with other RASopathies, such as cardio-facio-cutaneous syndrome (CFC), provides insight into the complexities of Ras/MAPK signaling in human craniofacial and dental development.

Key words: Costello syndrome; CS; craniofacial development; malocclusion; MAPK pathway; occlusion; Ras; RASopathy; receptor tyrosine kinase; signal transduction; tooth development; gingival hyperplasia; enamel

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INTRODUCTION

Costello syndrome (CS) is characterized by craniofacial malformations, dermatologic anomalies, cardiac defects, musculoskeletal abnormalities, growth delay, and cognitive deficits [Rauen, 2007]. CS is one of the RASopathies, a group of conditions that includes neurofibromatosis type 1 (NF1), Noonan syndrome (NS), NS with multiple lentigines, capillary malformation-AV malformation syndrome, Legius syndrome, and Cardio-facio-cutaneous syndrome (CFC) [Tidyman and Rauen, 2009]. The RASopathies are caused by mutations that increase signaling through the Ras pathway, including the effector cascades triggered by mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) [Tidyman and Rauen, 2009]. In the case of CS, nearly all patients have a heterozygous, de novo germline mutation in *HRAS* that results in a constitutively active protein [Aoki et al., 2005; Estep et al., 2006].

Distinct mutations in the Ras/MAPK pathway result in different RASopathies that have both unique and overlapping phenotypic features, especially in the craniofacial complex. Geneticists rely on

Katherine A. Rauen and Ophir D. Klein are co-senior authors.
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Cyril Charles's present address is: is Team "Evo-Devo of Vertebrate Dentition", Institut de Génomique Fonctionnelle de Lyon, Ecole Normale Supérieure de Lyon, Université de Lyon, CNRS UMR 5242, Lyon, France
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*Correspondence to:
Ophir D. Klein, M.D., Ph.D., Department of Orofacial Sciences, University of California at San Francisco, 513 Parnassus Ave, HSE1509, San Francisco, CA 94143.
E-mail: ophir.klein@ucsf.edu
**Correspondence to:
Katherine A. Rauen, M.D., Ph.D., Department of Pediatrics, UCSF Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco, 2340 Sutter Street, Room S429, Box 0706, San Francisco, CA 94115.
E-mail: rauenk@peds.ucsf.edu
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craniofacial characteristics to clinically diagnose and guide genetic testing; however, distinguishing between RASopathies, such as CS and CFC, can prove difficult because of the shared phenotypic features. Thus, it is critical to carefully delineate the specific craniofacial characteristics of each of these syndromes.

Signaling through receptor tyrosine kinases (RTKs), upstream of Ras/MAPK, plays a crucial role in craniofacial and dental development. For example, Fibroblast growth factors (Fgfs) that initiate signaling through RTKs are involved in the crosstalk between epithelium and mesenchyme that guides the formation of the craniofacial complex and the organs within it, including the teeth [Pispa and Thesleff, 2003; Nie et al., 2006]. Comparing the craniofacial and dental phenotypes of the RASopathies is important for our understanding of the role of Ras/MAPK signaling in craniofacial and dental development. We have recently reported the craniofacial and dental findings in CFC subjects [Goodwin et al., 2013a]. In order to refine the RASopathy phenotypes and to further our understanding of Ras/MAPK signaling in the craniofacial complex, we examined the craniofacial and dental features in 41 CS individuals, the largest such cohort examined to date for craniofacial analysis.

METHODS

The methods used in this study were similar to our previous report of the craniofacial and dental findings in CFC [Goodwin et al., 2013a]. This study was approved by the UCSF Committee on Human Research (IRB # 10-01426). A total of 41 individuals with a clinical diagnosis of CS were examined during the 6th International Costello Syndrome Conference in Berkeley, California in 2009 [Rauen et al., 2010] and the 7th International Costello Syndrome Family Forum in Chicago, Illinois in 2011. The diagnosis was confirmed by a board certified medical geneticist (K.A.R. or O.D.K.) based on clinical features. All of the 41 participants (21 males and 20 females) enrolled in our study were *HRAS* mutation positive. The average age of the cohort was 12.5 years, with a range of 1–35 years of age. The majority of the cohort reported Caucasian race (80%), but Latino (10%), African (5%), Asian (2%), and Middle Eastern (2%) individuals were also included. Written informed consent was obtained for all subjects. Complete intra- and extra-oral exams were performed by a licensed dentist (A.F.G., S.O., or J.M.). Exams included extra-oral frontal and profile view facial photographs. When possible, intra-oral photographs were taken, radiographs (including panoramic, periapical, and bitewing radiographs) and dental records provided by the participant were reviewed, and alginate dental impressions were taken. The total number of patients examined for each dental characteristic is listed in Table II. Statistical comparisons between the dental phenotypes of the CS cohort and CFC cohort or general U.S. population as determined by the NHANES III survey [Proffit et al., 2006] were made using the Fisher's exact test with two-tailed *P*-value.

RESULTS

Craniofacial Phenotype in CS

Individuals with CS have a characteristic craniofacial phenotype (Table I, Fig. 1). The majority (>50%) of subjects presented with relative macrocephaly (93%), high forehead (85%), and bitemporal narrowing (98%). A convex facial profile was a common finding (85%). Most subjects had a hyperteloric (56%) and telencanthic (83%) appearance. Most CS individuals had a short nose (73%) with a depressed nasal bridge (73%) and wide nasal tip (90%). Individuals with CS also had full cheeks (71%), large mouth (76%), and thick vermillion to upper lips (95%), often with a tented upper lip (76%). Commonly in CS, ears were low-set (93%) and posteriorly rotated (73%) with upturned lobes (66%).

TABLE I. Summary of Craniofacial Findings in a Cohort of 41 Individuals With Costello Syndrome (CS)

Craniofacial findings	n	%
Relative macrocephaly	38	93
High forehead	35	85
Bitemporal narrowing	40	98
Convex facial profile	33	85
Hyperteloric appearing	23	56
Telecanthic appearing	34	83
Depressed nasal bridge	30	73
Short nose	30	73
Wide nasal tip	37	90
Full cheeks	29	71
Large mouth	31	76
Thick vermillion to upper lips	39	95
Tented upper lip	31	76
Low-set ears	38	93
Posteriorly rotated ears	30	73
Upturned lobes	27	66

Dental Phenotype in CS

We identified a recognizable and distinct dental phenotype in CS (Table II, Fig. 2, Supplemental Table SI in supporting information online). An anterior open bite, a condition in which the anterior teeth are not in contact with the posterior teeth in occlusion, was a common vertical malocclusion observed in 41% of our cohort (Fig. 2B), an incidence significantly higher than the national average (3%; $P = 0.0001$). In contrast, a deep bite, when the maxillary anterior teeth overlap the mandibular teeth by greater than 2 mm, was significantly less common among our subjects (9%) than in the general population (49%; $P = 0.0001$). Posterior crossbite, a dental malocclusion in which the maxillary posterior teeth are positioned lingually (i.e., toward the tongue) relative to mandibular teeth (normally, maxillary teeth are placed bucally [i.e., toward the cheek]), was significantly more common in the CS cohort (35%; Fig. 2B) than in the general U.S. population (9%; $P = 0.0001$).

The Angle's classification system describes the relationship between the maxillary and mandibular first molars [Riolo, 2003]. Class I molar relationship is the ideal molar relationship in which the mesiobuccal (anterior, cheek side) cusp of the maxillary first molar aligns with the buccal side groove in the middle of the mandibular first molar so that the maxillary first molar and mandibular first molar are aligned. In class II molar relationship, the maxillary first

TABLE II. Summary of Dental Characteristics in Costello Syndrome (CS) and Cardio-Facio-Cutaneous Syndrome (CFC)

	CS			CFC						
Dental findings	Affected	Total examined[a]	%	Affected	Total examined[a]	%	General population[b] (%)	CS *P*-value[c]	CFC *P*-value[c,d]	CFC vs. CS *P*-value[e]
Malocclusion										
Vertical										
Anterior open bite	13	32	41	10	27	37	3	0.0001*	0.0001*	0.79
Deep bite	3	34	9	5	27	19	49	0.0001*	0.0001*	0.44
Transverse										
Posterior crossbite	12	34	35	4	21	19	9	0.0001*	0.032*	0.23
Anterior/posterior/sagittal										
Molar relationship										
Class I	8	27	30	7	13	54	41	0.139	0.089	0.17
Class II	9	27	33	6	13	46	53	0.006*	0.396	0.50
Class III	10	27	37	0	13	0	6	0.0001*	0.029*	0.016*
Arch perimeter										
Crowding	13	33	39	8	32	25	60	0.004*	0.0001*	0.29
Spacing	14	33	42	7	32	22	N/A[f]			0.11
Dental development										
Missing teeth	0	31	0	1	31	3	N/A			1.00
Supernumerary teeth	1	31	3	0	31	0	N/A			1.00
Delayed development	5	6	83	0	2	0	N/A			0.11
Delayed eruption	23	26	88	4	32	13	N/A			0.0001*
Hard tissue										
High palate	27	32	84	16	20	80	N/A			0.72
Thickening of the posterior maxillary alveolar ridge	10	33	30	0	31	0	N/A			0.0009*
Thickening of the anterior mandibular alveolar ridge	2	33	6	0	31	0	N/A			0.49
Soft tissue										
Gingival hyperplasia	21	33	64	1	31	3	N/A			0.0001*
Pathology										
Caries present at exam	9	35	26	7	28	25	N/A			1.00
History of caries	10	14	71	4	7	57	N/A			0.64
Enamel defect	29	33	88	4	13	31	N/A			0.0003*
Habits										
Tongue thrusting	9	32	28	7	31	23	N/A			0.77
Open mouth posture	22	40	55	9	32	29	N/A			0.03*
Bruxism	18	32	56	3	31	10	N/A			0.0001*

*Significant *P*-value < 0.05.
[a]Number of CS or CFC individuals examined for each dental characteristic since dental exams were not completed on every individual in the cohort.
[b]Prevalence of dental characteristic in general population as determined by the NHANESIII survey [Proffit et al., 2006].
[c]Comparison of incidence of dental characteristic in CS or CFC cohort compared to general population using the Fisher's exact test with two-tailed *P*-value.
[d]Dental and craniofacial phenotype of CFC previously reported [Goodwin et al., 2013a].
[e]Comparison of incidence of dental characteristic between CS and CFC using the Fisher's exact test with two-tailed *P*-value.
[f]Data not available.

molar is positioned mesially (anteriorly in the mouth) to the mandibular first molar, while in class III molar relationship, the maxillary first molar is positioned distally (posteriorly) to the mandibular first molar. The percentage of CS subjects with class I molar relationship (30%) was not significantly different from the 41% of the U.S. population with class I molar relationship ($P = 0.139$). The percentage of subjects with class II molar relationship (33%) was significantly less than the national average (53%; $P = 0.006$), while class III molar relationship (37%) was significantly greater than the U.S. average (6%; $P = 0.0001$; Fig. 2A).

Dental crowding was only observed in 39% of our CS cohort compared to about 60% of the U.S. population ($P = 0.004$). None of the CS subjects presented with missing teeth, and only one subject presented with supernumerary teeth (lateral incisor), based on clinical examination and review of radiographs. Examination of panoramic X-rays for six CS patients indicated that dental development was delayed in five of the subjects. Eruption patterns were determined by assessing the teeth present in relationship to the age of the individual examined and comparing to the normal eruption pattern [Proffit et al., 2006]. Most CS individuals (88%) showed

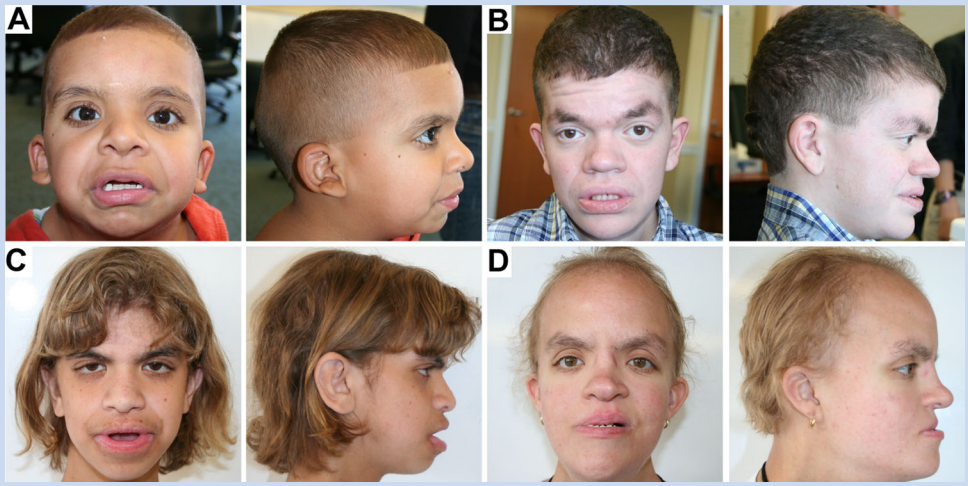

FIG. 1. Craniofacial phenotype in CS. Frontal and profile images of individuals with CS demonstrate the craniofacial phenotype. A: A 6-year-old boy with common CS craniofacial features including relative macrocephaly and short nose with depressed nasal bridge and wide nasal tip. B: A 20-year-old male with a convex facial profile and low-set, posteriorly rotated ears with upturned lobes. C: A 14-year-old female with full cheeks and a large mouth with thick vermillion to upper lips. D: A 23-year-old female with a high forehead, bitemporal narrowing, and hypertelloric and telecanthic appearance typical of CS.

delayed eruption patterns. The majority of subjects had a constricted high palate (84%; Fig. 2C). CS patients also presented with a thickening of the posterior maxillary alveolar ridge (30%; Fig. 2C), and two patients had a striking thickening of the anterior mandibular alveolar ridge (Fig. 2D). Most CS individuals had gingival hyperplasia (64%). Only 26% of CS individuals presented with clinical caries at exam; however, 71% had a history of caries according to dental records. Nearly all of the CS subjects presented with an enamel defect (88%), which was characterized clinically by demineralized white focal and striation lesions in the enamel. The patients who presented with enamel defects were 5–35 years of age while those who did not present with enamel defects tended to be younger, between the ages of 2 and 8. Subjects also presented with habits including a secondary tongue thrust (28%) and open mouth posture (55%). In addition, bruxism, as determined clinically by pathologic wear of the teeth, was present in 56% of our cohort.

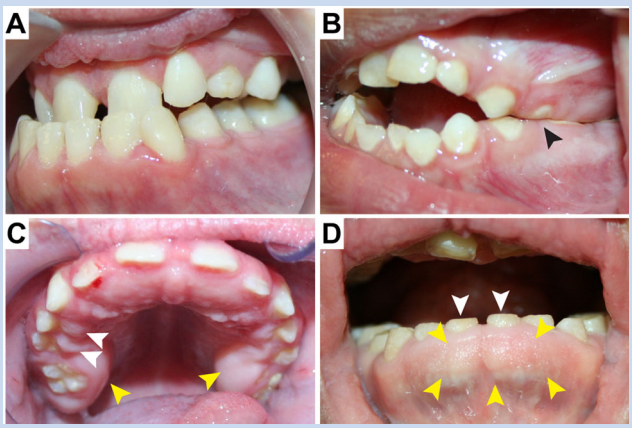

FIG. 2. Dental phenotype in CS. Intra-oral photographs show the typical dental phenotype in CS. A: Class III malocclusion. B: Open bite and posterior crossbite on the patient's left side marked by the black arrow. C: High palate with thickening of the posterior maxillary alveolar ridge (yellow arrows) and gingival hyperplasia (white arrows) typical of CS. D: Thickening of the anterior mandibular alveolar ridge (yellow arrows) and heavy incisal wear on the mandibular central incisors (white arrows).

DISCUSSION

The RASopathies are a group of syndromes caused by dysregulation of the Ras/MAPK pathway, and affected individuals commonly present with craniofacial dysmorphia. Each syndrome is characterized by distinct facies that are used to clinically differentiate and diagnose the many RASopathies. We have previously reported that CFC, caused by activating mutations in *KRAS*, *BRAF*, *MEK1*, or *MEK2* [Niihori et al., 2006; Rodriguez-Viciana et al., 2006], is characterized by a craniofacial phenotype that includes macrocephaly, bitemporal narrowing, convex facial profile, and hypoplastic supraorbital ridges [Goodwin et al., 2013a]. Here, we have thoroughly examined the craniofacial findings in CS, which is caused by heterozygous de novo germline mutations in the small GTPase HRAS that functions upstream of the kinases BRAF, MEK1, and MEK2. Individuals with CS share craniofacial features with CFC, including macrocephaly, bitemporal narrowing, and convex facial profile, but they also have additional, unique characteristics including full cheeks, large mouth, and thick vermillion to upper lips. The coarser appearance of CS individuals may be attributed to these fuller features, which are distinguishable from CFC, especially as individuals age. Analyzing the craniofacial features

of the RASopathies provides specific criteria that are useful in clinical diagnosis of the RASopathies, and further study may elucidate the role of Ras/MAPK signaling in craniofacial development.

There are many striking differences between the dental phenotypes of CS and CFC (Table II, Supplemental Table SI in supporting information online), and analysis of the dental phenotypes of the RASopathies caused by mutations in different components of the Ras pathway will provide insight into the role of Ras and its effector pathways in tooth development. In addition, specific tooth phenotypes may be utilized as diagnostic markers. We identified some overlapping dental characteristics between CS and CFC, but overall, CS had more dysmorphic dental characteristics compared to CFC. Malocclusion was a common dental finding in both CS and CFC, and there was no statistically significant difference in the incidence in anterior open bite or posterior crossbite between CS and CFC ($P = 0.79$ and 0.23, respectively, Table II). However, individuals with CS had a significantly increased incidence of class III molar relationship compared to CFC individuals and the general population ($P = 0.016$ and 0.0001, respectively). Similar to individuals with CFC, those with CS did not have anomalies in tooth number or morphology. Although we did not observe differences in size of the teeth clinically or based on dental casts ($n = 3$) in our CS cohort, it was recently reported in a small cohort of four CS individuals that primary lateral incisors and first and second molars and permanent first molars were small in size, based on multi-detector row computed tomography (MDCT) [Takahashi and Ohashi, 2013].

Our previous analyses of mice carrying mutations in RTK antagonists revealed the formation of supernumerary teeth and changes in tooth morphology due to hyperactive MAPK signaling [Klein et al., 2006, 2008; Peterkova et al., 2009]. We therefore had predicted that individuals with CS and CFC would have supernumerary or malformed teeth, and our finding of normal tooth number and shape was surprising. Another surprising finding was that in CS individuals the enamel structure was severely disrupted. Individuals with CS frequently presented with white focal lesions and striations (88%) [Goodwin et al., 2013b] compared to CFC individuals (31%; $P = 0.0003$). CS individuals also had increased incidence of attrition due to bruxism (56%) compared to CFC individuals (10%; $P = 0.03$), we suspect, due to increased susceptibility to pathologic wear due to decreased mineralization of CS enamel. The structure of CS enamel was less densely mineralized and disorganized when examined by scanning electron microscopy (SEM) [Goodwin et al., 2013b]. Interestingly, examination and SEM imaging of CFC enamel revealed normal structure (Goodwin et al. [2013a] and data not shown).

In addition to structural defects, CS individuals also had delayed tooth development and eruption, unlike CFC individuals. The difference in incidence of delayed tooth eruption was statistically significant between the CS and CFC cohorts ($P = 0.0001$), but there was no statistically significant difference in delayed tooth development ($P = 0.11$), most likely due to the small sample size of the cohorts (5/6 and 0/2, respectively; Table II). The delayed eruption in CS individuals may be due to dysfunction of osteoclasts, which resorb alveolar bone around the developing tooth to allow eruption [Wise, 2009]. CS and CFC individuals have been shown to have increased urinary pyridinium crosslinks (breakdown product of mature collagen), suggestive of increased osteoclastic activity [Stevenson et al., 2011]. However, activity of CS or CFC osteoclasts has not been assessed in vitro or in vivo. In addition to the osteoclast activity in the coronal region of the erupting tooth, there must also be osteogenic activity near the roots of the tooth to force the tooth to erupt and maintain alveolar bone around the tooth. Thus, tooth eruption requires both osteoclastic and osteogenic activity, and it may be that an imbalance in bone remodeling in the activated Ras signaling environment results in impairment of tooth eruption.

CS individuals presented with distinct hyperplasia of the oral tissues not observed in CFC. About 65% of our CS cohort and only 3% of our CFC cohort presented with gingival hyperplasia ($P = 0.0001$, Table II). A significant number (30%) of CS individuals also had thickening of the maxillary posterior alveolar ridge not observed in CFC (0%; $P = 0.0009$), and there were two CS individuals who presented with a thickening of the mandibular anterior alveolar ridge; this tissue hyperplasia was not correlated with prescription medications. It is intriguing that only CS and not CFC individuals presented with this tissue hyperplasia phenotype. Since CFC is mainly caused by mutations in MAPK (*BRAF*, *MEK1*, *MEK2*) and CS is caused by upstream activating mutations in HRAS, it is possible that Ras is signaling through PI3K, rather than MAPK, to increase oral tissue proliferation in CS. This hypothesis is supported by case reports in Proteus syndrome, a rare hamartoma syndrome that includes gingival hypertrophy and can be caused by mutations in the PI3K/AKT pathway [Becktor et al., 2002; Sakamoto et al., 2010]. Additionally, gingival fibromas have been reported in individuals with Tuberous Sclerosis caused by mutations in *TSC1* or *TSC2*, which encode proteins downstream of AKT [Sparling et al., 2007]. Activation upstream of Ras signaling has also been implicated in gingival hypertrophy, as in hereditary gingival fibromatosis type 1 (HGF1), which is caused by activating mutations in *SOS1*. This gene encodes a protein that recruits Ras to the membrane for activation, and gain of function leads to benign, slowly progressive, fibrous enlargement of maxillary and mandibular keratinized gingiva [Hart et al., 2002]. These data suggest differences in the roles of the multiple effector pathways of Ras such as MAPK and PI3K in the presentation of RASopathies.

Like individuals with CFC, CS individuals do not present with dental features requiring special treatment. CS individuals should receive regular dental exams and treatment with a general or pediatric dentist. Dentists should pay special attention to the oral hygiene of CS patients, as hyperplasia of the gingival tissue may make proper cleaning of the teeth difficult. Although the caries incidence in our cohort was not strikingly high, CS individuals may be at higher risk due to hypomineralized enamel. Increased fluoride treatment, whether in office fluoride varnish or at home fluoride rinse in addition to fluoride toothpaste, may be recommended. Additionally, hypomineralized enamel may lead to increased pathologic wear of the teeth due to bruxism, and for severe tooth abrasion, a custom mouthguard may be considered. Delayed tooth development and eruption should be explained to patients and their families to alleviate any concerns. If there is a significant delay in eruption, panoramic X-rays are recommended to determine tooth development stage. In addition, CS individuals are likely to develop

malocclusion, and early referral to an orthodontist is recommended. Especially in the case of class III malocclusion, initiating early orthodontic treatment during the mixed dentition phase, including expansion and protraction of the maxilla, may prevent the need for surgery.

Together, the data we present add to the study of the craniofacial and dental phenotypes in the RASopathies. We suggest that dental phenotypes, especially class III malocclusion, enamel hypo-mineralization, and soft tissue hyperplasia, may be used to distinguish CS from CFC, and further studies determining the dental phenotypes in the RASopathies and other syndromes may elucidate distinct oral phenotypes that could be utilized for clinical diagnosis. Additionally, comparing the RASopathies and focusing on the differences between the syndromes can help dissect the roles of the Ras pathway and its multiple effectors in craniofacial and dental development.

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