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ORIGINAL ARTICLE

Caregiver-reported dental manifestations in individuals with genetic neurodevelopmental disorders

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Abstract

Background: Children with neurodevelopmental disorders (NDDs) often have poor oral health and dental abnormalities. An increasing number of genes have been associated with neurodevelopmental conditions affecting the oral cavity, but the specific dental features associated with many genes remain unknown.

Aim: To report the types and frequencies of dental manifestations in children with neurodevelopmental conditions of known genetic cause.

Design: A 30-question survey assesing ectodermal and dental features was administered through Simons Searchlight, with which formed a recontactable cohort of individuals with genetic NDDs often associated with autism spectrum disorder (ASD).

Results: Data were collected from a largely paediatric population with 620 affected individuals across 39 genetic conditions and 145 unaffected siblings without NDDs for comparison. Drooling, difficulty accessing dental care, late primary teeth eruption, abnormal primary and permanent teeth formation, misshapen nails, and hair loss were more frequent in individuals with NDDs. Additionally, we evidenced an association between three new pathogenic gene variant/oral manifestation pairs: *CSNK2A1*/unusual primary teeth, *DYRK1A*/late primary teeth eruption, and *PPP2R5D*/sialorrhea.

Conclusion: Our results demonstrate that genetic NDDs caused by mutations in *CSNK2A1*, *DYRK1A*, and *PP2R5D* are associated with unique dental manifestations, and knowledge of these features can be helpful to personalize dental care.

KEYWORDS

brain function, dental health survey(s), genetics, personalized medicine, tooth development

1 | INTRODUCTION

Neurodevelopmental disorders (NDDs) are a group of neurologic conditions that include intellectual disability (ID), autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), communication disorders, and other conditions that affect brain development.[1] This definition encompasses many distinct diagnoses, and some associated medical features overlap, yet some are unique. With the ability to genetically stratify NDDs, we can refine clinical care based on the unique features associated with each genetic condition.[2]

One of the healthcare challenges for children with NDDs is an ~40% likelihood of oral health problems[3] including a higher prevalence of caries, gingivitis, and extractions.[4] Difficulty maintaining proper oral care has

been attributed to behavioral challenges including brushing requiring significant assistance, oral sensory sensitivity, self-injurious behavior leading to trauma, and lack of cooperation during dental visits.[5,6] Iatrogenic xerostomia and gingival hyperplasia due to the use of antidepressants, anxiolytics, and anticonvulsants can also make proper dental care more difficult for children with NDDs. The mechanism of action of decreased salivary flow includes anticholinergic medications, whereas it is hypothesized that the destruction of metalloproteinases by medications is responsible for gingival hyperplasia.[7,8]

Other observed dental abnormalities such as ectopic eruptions, shape and positional anomalies, hypodontia, and anterior open bites[9] suggest a developmental disruption driven by genetic factors. NDDs are highly heterogeneous, and the greater accessibility of genomic tools such as exome/genome sequencing and large genetic studies have identified hundreds of genes associated with NDDs. A number of these genes converge on common developmental pathways important for the normal development of dentition such as Sonic hedgehog (Shh) or Wnt signaling.[10] Although dental defects have been described as diagnostic markers for a few specific conditions, such as tooth enamel defect for mutations in *CTBP1*[11] or taurodontia in KBG syndrome,[12] most studies examining the oral cavity in children with NDDs have not specified the underlying genetic causes.[13]

Our knowledge of the distinct dental features related to NDD genes, therefore, remains incomplete. The primary purpose of this study was to use parent-reported information to systematically collect, describe, and compare the oral manifestations in individuals with genetic NDDs associated with autism and ID.

Why this paper is important to paediatric dentists

- This study highlighted previously unknown associations between genetic NDDs and dental manifestations.
- This study evidenced parent-based information in the form of a survey as an effective way for clinicians and researchers to gather information about dental presentations for children with genetic conditions.
- It showed that genetic testing allows for more personalized dental care in children with neurodevelopmental conditions.

2 | MATERIALS AND METHODS

This cross-sectional noninterventional study was conducted via an online questionnaire administered to parents of individuals enrolled in Simons Searchlight. It was approved by the Institutional Review Board of Columbia University (IRB-AAAF3927). Inclusion criteria for the probands include diagnosis of a pathogenic or likely pathogenic variant in one of the Simons Searchlight genes/copy number variants. Exclusion criteria for the affected group were having a dual diagnosis for two or more neurodevelopmental conditions and, for analysis, rare neurogenetic conditions with only one patient in the group to protect participant privacy since they could be identifiable. All genetic diagnoses of the neurodevelopmental conditions were reviewed by a laboratory geneticist and a genetic counselor. Most monogenic variants in probands were de novo and therefore not expected to be present in an unaffected sibling. Therefore, inclusion criteria for unaffected siblings did not usually include genetic testing for monogenic conditions. Unaffected siblings, however, were tested in the case of copy number variants. The online survey was developed in collaboration with a paediatric dentist (SC) from the College of Dental Medicine at Columbia University and a clinical geneticist (WKC) from the Vagelos College of Physicians and Surgeons at Columbia University. The choice of anomalies and characteristics included in the survey was based upon all issues reported in discussions with parents across 39 genetic conditions.

The online questionnaire consisted of 30 questions covering ectodermal (dental, hair, and nail) abnormalities. An initial pilot study was conducted with parents in Simons Searchlight who took the survey and provided feedback to improve question clarity. The survey (Table S1) was modified to clarify ambiguities. Early eruption of the first tooth was defined as <5 months for primary dentition and <5 years for permanent dentition. Delayed eruption of the first tooth was defined as >12 months for primary dentition and >8 years for permanent dentition.[14]

The responses were analyzed as a whole across all conditions and then for each genetic condition separately. Frequencies were compared across conditions and with the comparison populations. Significance was determined by Fisher's exact test when the 2×2 contingency table contained an expected frequency <5 and by the chi-squared test for all other calculations. Statistical significance was set at a p-value <.05. Risk ratios were also calculated.

For each question, parents had the opportunity to respond with not applicable, not sure, or to leave it blank. These responses were tallied per trait. Additionally, the question regarding the development of second molars was limited to individuals who were at least 13 years old, the age at which second molars should have developed. These limitations ensured respondents were age-appropriate for each question.

3 | RESULTS

Responses were collected for a largely paediatric population of 620 individuals (526 children and 94 adults) across 39 genetic NDDs (Table S2). In addition, 145 siblings (144 children and 1 adult) across all conditions without an NDD served as a pooled comparison group. As the siblings come from the same families as the affected children, we expect a similar race/ethnicity and socioeconomic background. The survey was sent to parents of 2295 affected individuals with a response rate of 27% and 584 unaffected siblings with a response rate of 24.8%.

In the cohort of affected individuals, the average age was 11.4 years with a standard deviation of 11.0. The male:female ratio was 1.1:1. In the unaffected sibling comparison group, the average age was 8.2 years with a standard deviation of 4.7. The male:female sex ratio was 1.4:1 (Table 1). In order to account for the younger age profile of the sibling population, the comparison did not assess features that are highly age-dependent or manifest only in an older population. Specifically, the features that were excluded were the number of permanent teeth extracted and cavities in the permanent dentition.

There were 226 children who did not have any adult teeth and were therefore excluded from all calculations discussing permanent dentition: early or late eruption of adult teeth, abnormal permanent teeth, and the failed eruption of permanent teeth.

The frequency of each dental abnormality in all NDD individuals and in the 145 unaffected siblings is shown in Table 2. Drooling, difficulty accessing dental care, late primary teeth eruption, and abnormal primary and permanent teeth formation were significantly more frequent in the NDD group. Dry mouth, cleft palate, untreated cavities, failed eruption, fused teeth, delayed permanent eruption, primary extractions, early primary eruption, and primary cavities were not found significantly more in individuals with NDDs.

Extraoral ectodermal features present in all individuals with NDDs compared with the 145 unaffected siblings are shown in Table 2. Misshapen nails and hair loss were significantly more frequent in the individuals with NDDs, whereas abnormally thin or thick hair was not.

Survey responses were then analyzed separately for each of the 39 genetic conditions. Full results including counts and frequencies can be found in Table S2. The criterion for statistical significance was $p < .05$ when compared with the unaffected sibling cohort and with the cohort of individuals with other NDDs (Table 3). Of the 39 genes examined, four genes presented significant findings. Early primary tooth eruption was found to be associated with pathogenic variants in *ADNP*, a previously known finding. Additionally, pathologic variations in *CSNKA1*, *DYRK1A*, and *PPP2R5D* were associated with previously undescribed dental manifestations. A significantly higher frequency of dental anomalies was found in the primary dentition of children with *CSNK2A1*-related NDD. Dental malformations parents described included long incisors, cracked teeth, missing enamel, small teeth, and fused teeth (Table 4). Additionally, pathogenic variants in *DYRK1A* were associated with late primary teeth eruption and pathogenic variants in *PPP2R5D* were associated with sialorrhea.

TABLE 1 Age distribution and sex of individuals with neurodevelopmental disorders (NDDs) and siblings comparison group.

	Number and percentage of affected individuals with NDDs	Number and percentage of unaffected siblings in comparison group
Age (years)		
0–3	85 (13.7%)	29 (20%)
3–6	148 (23.9%)	24 (16.6%)
6–9	108 (17.4%)	24 (16.6%)
9–12	77 (12.4%)	34 (23.4%)
12–15	72 (11.6%)	18 (12.4%)
15–18	36 (5.8%)	15 (10.3%)
18–21	13 (2.1%)	0 (0.0%)
21–24	3/145 (2.1%)	0 (0.0%)
24+	0/26 (0.0%)	1 (0.7%)
Sex		
Male	325 (52.4%)	85 (58.6%)
Female	295 (47.6%)	60 (42.4%)

4 | DISCUSSION

Individuals with genetic NDDs are vulnerable to developing a range of dental conditions due to a combination of genetic and behavioral patterns.[4] Emphasis on oral hygiene is especially important for this population because many children with an ID or profound ASD remain nonverbal or minimally verbal and cannot easily communicate symptoms of oral pain.[15] Compounded with difficulty in cooperation due to increased anxiety about dental visits and hypersensitivity to sensory stimuli, many children with NDDs experience delays in diagnosing caries and other dental problems.[16]

The results of the survey reinforced known dental manifestations and characterized new gene-specific dental associations. Comparing all individuals with NDDs as a single cohort with the unaffected sibling comparison group highlights a significantly higher frequency of

TABLE 2 Dental and ectodermal findings in individuals with neurodevelopmental disorders (NDDs) vs. sibling comparison group.

Condition evaluated	Frequency in individuals with NDDs	Frequency in unaffected sibling comparison group	*p*-Values	Risk ratio (confidence interval)
Sialorrhea	201/619 (32.5%)	6/145 (4.1%)	<.0001	7.8 (3.6–17.3)
Dental care difficulty	123/614 (20.0%)	6/145 (4.1%)	<.0001	5.2 (2.4–11.6)
Abnormal primary teeth	52/612 (8.5%)	3/144 (3.2%)	.016	4.1 (1.3–12.9)
Late primary eruption[b]	40/497 (8.0%)	2/122 (1.6%)	.027	4.9 (1.2–20.0)
Abnormal adult teeth	46/394 (11.7%)	3/93 (2.1%)	.027	3.6 (1.2–11.4)
Dry mouth	25/619 (4.0%)	1/145 (.7%)	.082	5.9 (0.8–42.9)
Cleft palate	18/614 (2.9%)	0/145 (0.0%)	.13	8.8 (0.5–144.9)
Untreated cavity	31/612 (5.1%)	3/145 (2.1%)	.13	2.4 (0.8–7.9)
Failed eruption	17/156 (10.9%)	0/26 (0.0%)	.21	6.0 (0.4–97.2)
Fused teeth	13/578 (2.2%)	1/143 (.7%)	.26	3.2 (0.4–24.6)
Primary teeth extracted	149/573 (26.0%)	35/140 (25.0%)	.81	1.0 (0.8–1.4)
Late permanent eruption[d]	14/307 (4.6%)	3/76 (3.9%)	.82	1.2 (0.3–3.9)
Early permanent eruption[c]	26/307 (8.5%)	7/76 (9.2%)	.84	0.9 (0.4–2.0)
Early primary eruption[a]	83/497 (16.7%)	24/122 (19.7%)	.43	0.8 (0.6–1.3)
Primary cavities	167/613 (27.2%)	45/145 (31.0%)	.35	0.9 (0.7–1.2)
Misshapen nails	103/577 (17.9%)	4/144 (2.78%)	.0002	6.4 (2.4–17.2)
Hair loss	62/596 (10.4%)	2/144 (1.4%)	.005	7.5 (1.9–30.3)
Thick hair	124/615 (20.2%)	19/144 (13.2%)	.06	1.5 (1.0–2.4)
Thin hair	35/615 (5.7%)	3/144 (2.1%)	.09	2.7 (0.9–8.8)

[a]Early primary tooth eruption defined as the first tooth erupting before 5 months of age.

[b]Late primary tooth eruption defined as the first tooth erupting after 12 months of age.

[c]Early permanent tooth eruption defined as the first tooth erupting before 5 years of age.

[d]Late permanent tooth eruption defined as the first tooth erupting after 8 years of age.

drooling, difficulty accessing dental care, late primary teeth eruption, and abnormal growth of primary and permanent teeth. Lack of access to dental services has been well-documented for individuals with NDD and ID. Contributing factors include insufficient staff training and lack of equipment for alternative treatment plans involving general anesthesia.[4,17] Despite reported difficulties accessing services, our study did not find an increased number of untreated cavities in this population of children with NDDs. Additionally, previous studies have indicated that individuals with NDDs related to ASD may present increased rates of dental caries,[18] but this was not a significant finding in our study. Nonstatistically significant findings may be the result of some gene groups having small numbers of individuals and the signal being lost when pooled with the whole group of NDDs.

Many of the more frequent dental features are developmental in nature and likely due to the pleiotropic effects of the genes on the brain and other organs. Sialorrhea is common and has been associated with apraxia and hypotonia in children with NDDs.[19] The association of NDDs with abnormal primary and permanent dentition has been described in case reports but was not characterized across genetic conditions.[20] Late primary tooth eruption has not been previously described to be associated with neurodevelopmental conditions. Many individuals with NDDs have feeding and GI issues as part of their underlying condition, and dietary adjustments are numerous and complex to address these issues. The level of detail in the diet questions was inadequate to allow for analysis with dental outcomes.

Nonoral ectodermal features that were significantly more frequent include misshapen nails and hair loss. Developmentally, the brain, teeth, and nails are all derived from the ectoderm and are regulated by many of the same signaling pathways such as the Wnt, bone morphogenic protein (BMP), or fibroblast growth factor (FGF) pathways.[21] Case reports have highlighted the presence of neurodevelopmental delay along with teeth, hair, and nail abnormalities in the same individual.[22]

Characterizing specific NDDs based on the underlying genetic cause allowed us to highlight several findings. We replicated previously known dental abnormalities associated with pathogenic variants in *ADNP*, confirming the

TABLE 3 Summary of statistically significant dental findings across genetic conditions.

Genetic condition	Dental abnormality	Frequency in affected individuals in specified NDD	Frequency in unaffected sibling comparison group	*p*-Values	Risk ratio (confidence interval [CI])	Frequency in affected individuals in other NDDs	*p*-Values	Risk-ratio (CI)
ADNP	Early primary tooth eruption[b]	4/6 (66.7%)	24/122 (19.7%)	.02[a]	3.4 (1.7–6.6)	79/491 (16.1%)	.008[a]	4.1 (2.3–7.6)
CSNK2A1	Unusual primary teeth	6/14 (42.9%)	3/144 (2.1%)	<.00001[a]	20.6 (5.8–73.4)	50/598 (8.4%)	<.00001[a]	5.1 (2.6–9.9)
DYRK1A	Late primary tooth eruption[c]	7/13 (53.8%)	2/122 (1.6%)	<.00001[a]	32.8 (7.6–142.0)	35/484 (7.2%)	<.00001	7.4 (4.1–13.5)
PPP2R5D	High salivary flow	22/33 (66.7%)	6/145 (4.1%)	<.00001	16.1 (7.1–36.6)	179/568 (31.5%)	.00002	2.1 (1.6–2.8)

[a]Fisher's exact test is used when the 2×2 contingency table contains an expected frequency <5.
[b]Early primary tooth eruption defined as the first tooth erupting before 5 months of age.
[c]Late primary tooth eruption defined as the first tooth erupting after 12 months of age.

reliability of the parent-provided information to characterize oral features in children with NDDs. Early eruption of the primary dentition was previously described in 81% of patients with *ANDP*-related NDD ($n = 54$),[23] and we found early primary eruption in 66% of our cohort. Our findings confirm the relevance of early primary tooth eruption as a clinical marker for *ADNP* mutations.

We also described three previously unreported associations between genetic conditions and dental features: *CSNK2A1* and unusual primary teeth, *DYRK1A* and late primary tooth eruption, and *PPP2R5D* and drooling.

Pathogenic variants in *CSNK2A1* are associated with Okur–Chung neurodevelopmental syndrome. We found that these patients had a high frequency of abnormal primary dentition (42.9%) that has not been described previously (Table 4). In these six children, a range of teeth malformations were described, and no findings were recurrent. Further focused evaluations may help identify specific patterns of developmental dental defects. Given the frequency and variability of many of these malformations, close follow-up with paediatric dentists may be warranted to monitor for defects as the permanent dentition erupts. *CSNK2A1* encodes for the α subunit of the Casein kinase II (CK2) protein, which is involved in two major developmental pathways associated with tooth formation: Wnt signaling and NF-κB signaling. CK2 promotes the Wnt/β-catenin signal transduction pathway by phosphorylating β-catenin and the transcription factor TCF/LEF.[24] Knockout of the Wnt/β-catenin pathway has been shown to inhibit multiple stages of tooth morphogenesis in animal models.[25] Disruption of this pathway results in downregulation of bone morphogenetic protein 4 (BMP4) activity, which is required for the proper development of both molars and incisors.[26] The resulting dental defects include misshapen tooth buds[25] and defective enamel.[27] CK2 has also been shown to activate the inducible transcription factor NF-κB through phosphorylation of its inhibitor, IκB.[28] Previous animal model studies have demonstrated that the downstream signaling pathway associated with NF-κB affects early tooth development.[29] Disruptions of this signaling cascade in rat dental epithelial stem cells lead to abnormal tooth morphology such as an abnormal number of cusps.[30]

Delayed primary tooth eruption, which was defined as the first primary tooth erupting after 12 months of age, was reported in 53.8% of individuals with *DYRK1A*-related NDD. This association has been reported in an isolated case report, but its prevalence was not described.[31] The pathogenesis of delayed primary teeth eruption was not linked to hypothyroidism, which is associated with *DYRK1A* in four of 14 (28.6%) individuals.[32] Delay in initial teething affects speech production; diet due to the inability to chew certain foods is

TABLE 4 Primary teeth abnormalities in individuals with *CSNK2A1* variants.

Participant	Sex	Age (years)	Parent description of primary teeth abnormality
Individual 1	Male	6.4	Fused teeth
Individual 2	Female	8.5	Fangs (long incisors)
Individual 3	Female	13.6	Abnormal shape; all primary teeth had cavities before falling out
Individual 4	Female	13.8	Gum was growing around the primary tooth and covering it, tooth disintegrating, and cracking
Individual 5	Male	7.8	Enamel missing, deformation of a single tooth
Individual 6	Male	5.6	Small teeth; very slow to grow

associated with fewer erupted teeth at an older age[33] and can impact the overall functioning of these children. Delayed primary tooth eruption could serve as a clinical marker for the diagnosis of *DYRK1A*-related NDD.

This study demonstrated that sialorrhea is associated with other genetic NDD conditions when examined as a single group. Individuals with *PPP2R5D*-related NDD, however, had a significantly higher frequency of drooling (66%) than those with all other NDDs (31.5%). Our data did not indicate that sialorrhea affected the prevalence of caries in these individuals. Complications of excess salivary flow out of the mouth include perioral chapping, dehydration, and social stigmatization.[34] Management strategies for drooling are multidisciplinary, including noninvasive prosthetic devices and pharmacological methods or invasive modalities such as the removal of salivary glands or laser photocoagulation.[35] Drooling could be caused by pronounced hypotonia and developmental delays in gross motor skills associated with *PPP2R5D*-related NDD. Drooling is also associated with neurological conditions such as Parkinson's disease, cerebral palsy, or stroke.[36] Sialorrhea has not been previously reported for *PPP2R5D*-related NDD, and further investigation is warranted to explore the specific mechanism behind the association with drooling given that most children are not neurologically severely disabled.

The survey was tailored to be descriptive and provides an inventory of the features that may be seen in a wide variety of specific genetic diagnoses. Therefore, limitations of the study include the small and heterogeneous sample sizes for many of these rare genetic conditions. With small numbers of individuals for some conditions, our study may be underpowered to observe a statistical significance, especially if features are incompletely penetrant. This limitation may help to explain why the other 35 genes we evaluated did not display statistical enrichment when compared with both the sibling comparison group and the cohort of individuals with other NDDs. As more children are identified with these conditions, future studies with larger sample sizes may be able to demonstrate additional dental associations. Additional studies are also warranted given the overall survey response rate of 26.6%. Another limitation of the study is the age of the affected (mean age 8.2 years) and unaffected individuals (mean age of 11.4) for whom the surveys were completed. As most of the participants are children, manifestations at older ages are underrepresented and will benefit from longitudinal follow-up of this cohort. To address the older age of the unaffected siblings, this study did not compare highly age-dependent dental features such as the number of permanent teeth extracted and cavities in the permanent dentition.

Unmet dental care remains a significant healthcare issue for children with NDDs,[16] highlighting the need for tailored recommendations to improve the monitoring of these individuals. This study leveraged precise genotypic characterization of the cohort that includes a large number of genetic NDDs to associate previously unreported dental manifestations with NDDs, providing the foundation for future personalized dental management.

AUTHOR CONTRIBUTIONS

Deanna Noble and Wendy K Chung conceived the ideas; Deanna Noble and Steven Chussid designed the survey to collect the data; Neil R Ming and Alban Ziegler analyzed the data; and Neil R Ming led the writing.

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CONFLICT OF INTEREST STATEMENT

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Doernberg E, Hollander E. Neurodevelopmental disorders (asd and adhd): Dsm-5, icd-10, and icd-11. *CNS Spectr*. 2016;21(4):295-299.
2. Reddy MS, Shetty SR, Vannala V. Embracing personalized medicine in dentistry. *J Pharm Bioallied Sci*. 2019;11(Suppl 2):S92-S96.
3. Yusuf ZI, Dongarwar D, Yusuf RA, Salihu HM. Oral health problems among children with neurodevelopmental disorders in the United States. *Int J MCH AIDS*. 2020;9(1):157-160.
4. Wilson NJ, Lin Z, Villarosa A, George A. Oral health status and reported oral health problems in people with intellectual disability: a literature review. *J Intellect Develop Disabil*. 2019;44(3):292-304.
5. El Khatib AA, El Tekeya MM, El Tantawi MA, Omar T. Oral health status and behaviours of children with autism spectrum disorder: a case-control study. *Int J Paediatr Dent*. 2014;24(4):314-323.
6. Friedlander AH, Yagiela JA, Paterno VI, Mahler ME. The neuropathology, medical management and dental implications of autism. *J Am Dent Assoc*. 2006;137(11):1517-1527.
7. Mawardi H, Alsubhi A, Salem N, et al. Management of medication-induced gingival hyperplasia: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2021;131(1):62-72.
8. Scully C. Drug effects on salivary glands: dry mouth. *Oral Dis*. 2003;9(4):165-176.
9. Gandhi R, Ruxmohan S, Puranik CP. Association between autism spectrum disorder and dental anomalies of the permanent dentition. *Paediatr Dent*. 2021;43(4):307-312.
10. Jussila M, Thesleff I. Signaling networks regulating tooth organogenesis and regeneration, and the specification of dental mesenchymal and epithelial cell lineages. *Cold Spring Harb Perspect Biol*. 2012;4(4):a008425.
11. Beck DB, Cho MT, Millan F, et al. A recurrent de novo ctbp1 mutation is associated with developmental delay, hypotonia, ataxia, and tooth enamel defects. *Neurogenetics*. 2016;17(3):173-178.
12. Dowling PA, Fleming P, Gorlin RJ, King M, Nevin NC, McEntagart M. The kbg syndrome, characteristic dental findings: a case report. *Int J Paediatr Dent*. 2001;11(2):131-134.
13. Burgette JM, Rezaie A. Association between autism spectrum disorder and caregiver-reported dental caries in children. *JDR Clin Trans Res*. 2020;5(3):254-261.
14. Kjær I. Mechanism of human tooth eruption: Review article including a new theory for future studies on the eruption process. *Scientifica*. 2014;2014:1-13. doi:10.1155/2014/341905
15. Koegel LK, Bryan KM, Su PL, Vaidya M, Camarata S. Definitions of nonverbal and minimally verbal in research for autism: a systematic review of the literature. *J Autism Dev Disord*. 2020;50(8):2957-2972.
16. Lai B, Milano M, Roberts MW, Hooper SR. Unmet dental needs and barriers to dental care among children with autism spectrum disorders. *J Autism Dev Disord*. 2012;42(7):1294-1303.
17. Oliveira JS, Prado Junior RR, de Sousa Lima KR, de Oliveira AH, Moita Neto JM, Mendes RF. Intellectual disability and impact on oral health: a paired study. *Spec Care Dentist*. 2013;33(6):262-268.
18. Jaber MA. Dental caries experience, oral health status and treatment needs of dental patients with autism. *J Appl Oral Sci*. 2011;19(3):212-217.
19. Ming X, Brimacombe M, Wagner GC. Prevalence of motor impairment in autism spectrum disorders. *Brain and Development*. 2007;29(9):565-570.
20. Medina AC, Sogbe R, Gomez-Rey AM, Mata M. Factitial oral lesions in an autistic paediatric patient. *Int J Paediatr Dent*. 2003;13(2):130-137.
21. Patthey C, Gunhaga L. Signaling pathways regulating ectodermal cell fate choices. *Exp Cell Res*. 2014;321(1):11-16.
22. Zhou X, Khan SG, Tamura D, et al. Brittle hair, developmental delay, neurologic abnormalities, and photosensitivity in a 4-year-old girl. *J Am Acad Dermatol*. 2010;63(2):323-328.
23. Gozes I, Van Dijck A, Hacohen-Kleiman G, et al. Premature primary tooth eruption in cognitive/motor-delayed adnp-mutated children. *Transl Psychiatry*. 2017;7(2):e1043.
24. Wang H, Lv Q, Xu Y, et al. An integrative pharmacogenomics analysis identifies therapeutic targets in kras-mutant lung cancer. *EBioMedicine*. 2019;49:106-117.
25. Liu F, Chu EY, Watt B, et al. Wnt/beta-catenin signaling directs multiple stages of tooth morphogenesis. *Dev Biol*. 2008;313(1):210-224.
26. Fujimori S, Novak H, Weissenbock M, et al. Wnt/beta-catenin signaling in the dental mesenchyme regulates incisor development by regulating bmp4. *Dev Biol*. 2010;348(1):97-106.
27. Cantu C, Pagella P, Shajiei TD, et al. A cytoplasmic role of wnt/beta-catenin transcriptional cofactors bcl9, bcl9l, and pygopus in tooth enamel formation. *Sci Signal*. 2017;10(465):eaah4598.
28. Dominguez I, Sonenshein GE, Seldin DC. Protein kinase ck2 in health and disease: Ck2 and its role in wnt and nf-kappab signaling: linking development and cancer. *Cell Mol Life Sci*. 2009;66(11–12):1850-1857.
29. Ohazama A, Hu Y, Schmidt-Ullrich R, et al. A dual role for ikk alpha in tooth development. *Dev Cell*. 2004;6(2):219-227.
30. Liang Y, Chen G, Yang Y, et al. Effect of canonical nf-kappab signaling pathway on the differentiation of rat dental epithelial stem cells. *Stem Cell Res Ther*. 2019;10(1):139.
31. Van Bon BWM, Coe BP, De Vries BBA, Eichler EE. Dyrk1a syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. *Genereviews((r))*. University of Washington; 1993.
32. Ji J, Lee H, Argiropoulos B, et al. Dyrk1a haploinsufficiency causes a new recognizable syndrome with microcephaly,

intellectual disability, speech impairment, and distinct facies. *Eur J Hum Genet*. 2015;23(11):1473-1481.
33. Backstrom MC, Aine L, Maki R, et al. Maturation of primary and permanent teeth in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2000;83(2):F104-F108.
34. Hockstein NG, Samadi DS, Gendron K, Handler SD. Sialorrhea: a management challenge. *Am Fam Physician*. 2004;69(11):2628-2634.
35. Bavikatte G. Management of drooling of saliva. *Br J Med Pract*. 2012;5:5071.
36. Morgante F, Bavikatte G, Anwar F, Mohamed B. The burden of sialorrhoea in chronic neurological conditions: current treatment options and the role of incobotulinumtoxina (xeomin(r)). *Ther Adv Neurol Disord*. 2019;12:1756286419888601.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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