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Oral Findings of RASopathies in Children: Molecular Mechanisms and Clinical Spectrum with a Focus on Neurofibromatosis Type 1

Elif Kabacıoğlu[1], Nursel Elçioğlu[2], Funda Kökali[2], Ali Menteş[1]

[1]Department of Pediatric Dentistry, Marmara University Faculty of Dentistry, İstanbul, Türkiye
[2]Department of Pediatric Genetics, Marmara University Faculty of Medicine, İstanbul, Türkiye

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What is already known on this topic?

- *RASopathies comprise a broad collection of developmental disorders arising from germline alterations that disturb the RAS–MAPK signaling pathway, resulting in diverse clinical and genetic presentations.*
- *Neurofibromatosis type 1 (NF1) is the most frequently encountered condition within this group and is associated with marked multisystem involvement, including dermatologic, neurologic, cardiovascular, and skeletal features.*
- *Although oral and craniofacial involvement is part of the phenotypic spectrum, these features remain underdiagnosed and are often overlooked in routine clinical evaluation.*

What this study adds to this topic?

- *This review provides an updated synthesis of current knowledge on the molecular mechanisms, clinical spectrum, and diagnostic criteria of NF1 and related RASopathies.*
- *It emphasizes the clinical relevance of oral and craniofacial manifestations as early diagnostic indicators and their potential role in guiding multidisciplinary management strategies.*
- *By integrating recent advances in molecular pathogenesis with emerging targeted therapeutic approaches, this review outlines the ongoing developments in the clinical care of individuals with RASopathies.*

Abstract

RASopathies constitute a group of inherited disorders caused by germline alterations that affect the RAS–MAPK pathway, a signaling cascade essential for regulating cellular growth and development. Among these disorders, neurofibromatosis type 1 (NF1) represents the most frequently encountered form. Other related conditions—including Noonan syndrome, its lentiginous variant, Costello syndrome, cardio-facio-cutaneous syndrome (CFCS), Legius syndrome, and capillary malformation–arteriovenous malformation syndrome—demonstrate significant genetic and phenotypic overlap. This review offers current evidence on the molecular basis, clinical manifestations, oral findings, diagnostic approaches, and management strategies of NF1 and related RASopathies. A structured literature review was performed using PubMed, Scopus, and Web of Science databases, including publications available up to June 2024. RASopathies commonly present with craniofacial abnormalities, cardiac defects, neurodevelopmental delays, and cutaneous manifestations, though each syndrome varies in genetic origin and clinical expression. Neurofibromatosis type 1 remains the most frequent, while Costello and CFCSs are comparatively rare. Oral findings—such as high-arched palate, gingival enlargement, and jawbone lesions—may serve as useful early diagnostic indicators. Recent advances in genetic testing and the emergence of targeted molecular therapies have significantly refined diagnostic accuracy and patient care. Recognizing genotype–phenotype correlations and integrating oral with systemic features are key to timely diagnosis and comprehensive management. Multidisciplinary collaboration and precision-based approaches are essential to improve long-term outcomes for individuals affected by RASopathies.

Keywords: Cardio-facio-cutaneous syndrome, Costello syndrome, craniofacial abnormalities, MAP kinase signaling system, neurofibromatosis type 1, Noonan syndrome

Introduction

RASopathies comprise a spectrum of developmental syndromes that arise from inherited mutations in genes regulating the RAS–MAPK cascade, which plays a central role in regulating cellular proliferation, differentiation, and aging. Unlike the somatic variants responsible for tumorigenesis, these germline alterations exert their effects during embryogenesis, resulting in abnormal tissue development and multisystem involvement. Clinically, affected individuals often display shared features such as distinctive facial morphology, congenital cardiac defects, pigmentary or skeletal abnormalities, neurodevelopmental delay, hypotonia, and increased tumor susceptibility. The prevalence of RASopathies is approximated at about 1 per 1000 births.[1-4] This group encompasses conditions such as neurofibromatosis type 1 (NF1), Noonan syndrome (NS) and its lentiginous variant, Costello syndrome (CS), capillary malformation–arteriovenous malformation (CM–AVM) syndrome, cardio-facio-cutaneous syndrome (CFCS), and Legius syndrome (LS).[3]

The RAS–MAPK signaling module is among the most thoroughly defined intracellular pathways and has been the focus of extensive research in oncology due to its recurrent somatic alterations across multiple tumor types. RAS proteins (HRAS, KRAS, and NRAS) are small GTP-binding molecules (~21 kDa)

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Corresponding author: Elif Kabacıoğlu,Department of Pediatric Dentistry, Marmara University Faculty of Dentistry, İstanbul, Türkiye **e-mail:** elifkabacioglu@gmail.com
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that share approximately 85% sequence homology and are ubiquitously expressed in human tissues.[5] Among them, mutations in KRAS are most frequent (~85%), whereas NRAS and HRAS account for smaller proportions (around 15% and <1%, respectively).[6]

Methods

This study was conducted as a narrative review synthesizing current evidence on NF1 and other RASopathies, with a particular focus on clinical, oral, genetic, and management aspects. To provide an overview of the available literature, searches were conducted in PubMed, Scopus, and Web of Science for studies published up to June 2024.

The literature search included combinations of the following keywords: "RASopathies," "neurofibromatosis type 1," "Noonan syndrome," "Costello syndrome," "cardio-facio-cutaneous syndrome," "capillary malformation–arteriovenous malformation," "Legius syndrome," and "RAS–MAPK pathway."

Relevant publications included case series, clinical trials, narrative and systematic reviews, and clinical guidelines published in English. Reference lists of relevant articles were also manually screened to identify additional sources. Studies focusing exclusively on molecular oncology or non-human models were excluded unless they provided clinically relevant insights.

Information on genetic mechanisms, pathophysiology, clinical and oral manifestations, and therapeutic approaches was reviewed and synthesized to highlight both shared and distinct characteristics across RASopathies.

As this review was based solely on previously published data and did not involve human participants or animal experiments, ethics committee approval was not required.

Neurofibromatosis Type 1

Neurofibromatosis type 1 is an autosomal dominant hereditary disorder and one of the most clinically significant RASopathies, illustrating how dysregulation of the RAS–MAPK signaling pathway can result in a multisystem developmental phenotype.[7] Neurofibromatosis type 1 presents with a highly variable clinical spectrum and affects multiple organ systems.

Although penetrance is complete, expressivity varies widely, and mild cases may remain undiagnosed.[8] Based on current diagnostic criteria and genetic testing, the estimated prevalence is approximately 1 in 2000 newborns, with no significant ethnic differences.[4]Approximately half of NF1 cases are inherited, while the remainder arise from de novo mutations, most commonly of paternal origin.[9]Neurofibromatosis type 1 has also been associated with increased mortality.[10,11]

Genetics of Neurofibromatosis Type 1

The *NF1* gene, located on chromosome 17q11.2, encodes neurofibromin, a tumor suppressor protein that plays a key role in regulating the RAS–MAPK signaling pathway.[12,13]Neurofibromin functions as a RAS GTPase–activating protein, thereby negatively modulating RAS activity and controlling cellular growth and differentiation.[5,14]

Germline mutations in the *NF1* gene result in a multisystem developmental disorder with overlapping features shared by other RASopathies driven by dysregulation of the RAS–MAPK pathway.[5] Loss of *NF1* function has also been implicated in tumorigenesis, supporting the link between developmental abnormalities and oncogenic processes in NF1.[15,16]

Molecular Diagnosis and Genotype–Phenotype Correlations in Neurofibromatosis Type 1

The diagnostic criteria for NF1 were originally established by the National Institutes of Health (NIH) in 1987 and have since been revised to incorporate molecular genetic testing.[8,17] As clinical diagnostic features may be absent or incomplete in early childhood, molecular testing has become an important tool for early and reliable diagnosis in pediatric patients.[18,19]

The earliest clinical manifestation of NF1 commonly includes café-au-lait macules (CALMs).[20,21] Genotype–phenotype correlations have been reported, particularly in patients with *NF1* microdeletions, who often exhibit an earlier onset and a more severe clinical presentation.[22] Nevertheless, the clinical expression of *NF1* remains highly variable and is influenced by the underlying genetic mutation.

Diagnostic Criteria for Neurofibromatosis Type 1

1987 National Institutes of Health Diagnostic Criteria

The diagnostic criteria for NF1 were first established during the 1987 NIH Consensus Conference.[8] A clinical diagnosis is made when at least 2 characteristic features are present, including CALMs, axillary or inguinal freckling, optic pathway glioma, Lisch nodules, neurofibromas or plexiform neurofibroma, distinctive osseous lesions, or a positive family history.

Using these criteria, NF1 can be diagnosed in approximately half of sporadic cases and in most familial cases during early childhood; however, in many sporadic patients, definitive diagnosis may be delayed until later childhood due to the age-dependent emergence of clinical manifestations.[7,18]

2021 Revised Diagnostic Criteria

In 2021, the diagnostic criteria for NF1 were revised to incorporate advances in molecular genetics and clinical assessment.[17] In individuals without an affected parent, a diagnosis can be established when 2 or more characteristic features are present, including CALMs, axillary or inguinal freckling, neurofibromas or plexiform neurofibroma, optic pathway glioma, Lisch nodules or choroidal abnormalities, distinctive skeletal lesions, or the identification of a pathogenic *NF1* variant.

In individuals with an affected parent, the presence of any one of these features is sufficient to establish the diagnosis.

Clinical Manifestations of Neurofibromatosis Type 1

Cutaneous Manifestations

Café-au-lait macules are the earliest and most common cutaneous manifestation of NF1 and typically appear during early childhood. They are characterized by homogeneous, light-brown, well-demarcated macules, and although not pathognomonic, their presence—particularly when associated with axillary or inguinal freckling—strongly supports the diagnosis.[20,23]

Neurofibromas are benign Schwann cell–derived tumors that may be cutaneous, subcutaneous, or plexiform in type. Cutaneous neurofibromas usually present as soft nodules, whereas plexiform neurofibromas are often congenital and may cause significant morbidity due to progressive growth, disfigurement, and potential malignant transformation.[5,20,24,25]

Ocular Manifestations

Ocular manifestations are common in NF1. Lisch nodules, which represent iris hamartomas, increase in number with age and are considered a characteristic diagnostic feature, although they typically do not affect visual acuity.[7,17]

Optic pathway gliomas occur in a subset of patients and may lead to visual impairment, particularly in childhood. Plexiform

neurofibromas involving the eyelid or orbit can cause facial asymmetry, visual disturbances, and functional impairment, and may carry a risk of malignant transformation.[5,7,26] Choroidal abnormalities, detectable using optical coherence tomography or near-infrared imaging, are currently recognized as supportive diagnostic features of NF1.[17]

Skeletal Manifestations

Skeletal manifestations are common in NF1 and include characteristic findings such as cranial dysplasia, long-bone deformities with a risk of pseudarthrosis, scoliosis, and short stature. Reduced bone mineral density has also been reported, although its clinical significance remains unclear.[7,25]

Cardiovascular Complications

Cardiovascular involvement represents an important source of morbidity in NF1 and includes vascular abnormalities, hypertension, and congenital cardiac defects. These findings reflect the central role of RAS–MAPK pathway dysregulation in cardiovascular development and vascular integrity.[25,27]

Gastrointestinal, Pulmonary, and Hematological Complications

Neurofibromatosis type 1 may also be associated with gastrointestinal, pulmonary, and hematological complications that contribute to systemic morbidity. These include gastrointestinal and intrathoracic tumors, pulmonary involvement, and hematological malignancies, reflecting the widespread effects of dysregulated RAS signaling across multiple organ systems.[5,25,28]

Neurological Manifestations

Neurological manifestations constitute a major source of morbidity in individuals with NF1. Common features include cognitive impairment, learning difficulties, attention-deficit/hyperactivity disorder, and other neurodevelopmental disorders, all of which may significantly affect academic performance and daily functioning.[7,23]

Epilepsy and intracranial tumors are also reported in a subset of patients and further contribute to the neurological burden of the disease.[7,29] Overall, neurological involvement plays a substantial role in shaping the clinical course and quality of life of individuals with NF1.

Oral Manifestations

Gingival Enlargement: Gingival enlargement is a recognized oral manifestation of NF1 and may be observed from childhood onward. It is attributed to increased cellularity within the gingival tissues and typically presents as a painless, localized, and non-inflammatory swelling. Such findings may raise clinical suspicion, particularly when encountered in pediatric patients without obvious local etiologic factors. Additional dental anomalies, including tooth agenesis, delayed eruption, impaction, and malposition, have been reported with variable frequency and may further complicate occlusal development.[30,31]

Melanin pigmentation of the gingiva has also been described, albeit infrequently. When present, it is usually symmetrical and persistent and appears to be independent of age, sex, or ethnic background.[30,31] An illustrative example is shown in Figure 1.

Neurofibromas and Other Oral Lesions: Both oral and perioral soft tissues may exhibit diverse alterations in individuals with NF1, including localized or plexiform neurofibromas, periodontal involvement, and dental morphological anomalies. Reported findings include supernumerary teeth, impaction, Class 3 molar relationships, and midline diastema, often accompanied by enlargement of the alveolar process.[10] These features may be detected during routine dental examinations and, in some cases, represent early indicators of the underlying condition.



Figure 1. Intraoral clinical photograph of a 13-year-old male with neurofibromatosis type 1 demonstrating gingival melanin pigmentation of the gingiva. The image was obtained from the authors' clinical archive, and written informed consent for publication was obtained from the patient's parents.

Plexiform neurofibromas may involve the maxilla or mandible, leading to facial asymmetry, functional impairment, or disturbances in mastication and speech. Although malignant transformation is uncommon, its potential underscores the importance of early recognition and long-term follow-up.[10] The tongue may also be affected, with neurofibromas or plexiform variants causing macroglossia and enlargement of fungiform papillae, which can interfere with oral function and hygiene.[30,31]

Mandibular and Radiographic Alterations: Mandibular skeletal changes are well documented in NF1 and may include widening of the mandibular foramen, enlargement of the coronoid and sigmoid notches, and posterior concavities along the mandibular border. These alterations may result from localized neurofibroma infiltration or developmental bone anomalies and are often detected incidentally on panoramic radiographs.[31]

Representative panoramic radiographic findings demonstrating multiple supernumerary teeth in the maxillary and mandibular jaws are shown in Figure 2, while delayed eruption associated with supernumerary teeth is illustrated in Figure 3. Although a direct association between NF1 and dental caries has not been conclusively established, dental developmental disturbances and challenges in maintaining optimal oral hygiene may contribute to an increased caries risk in affected children.[31]

Differential Diagnosis of Neurofibromatosis Type 1

Several inherited conditions may mimic NF1 due to the presence of CALMs and overlapping cutaneous or systemic features. Legius syndrome represents the most important differential diagnosis, as it is characterized by CALMs and axillary freckling but lacks neurofibromas, Lisch nodules, and central nervous system tumors.[32]

Other conditions to consider include NS, which may present with lentigines, short stature, congenital cardiac anomalies, and characteristic craniofacial features, as well as piebaldism and fibrous dysplasia/McCune–Albright syndrome, which may show pigmentary skin changes that can resemble CALMs.[25,33]



Figure 2. Panoramic radiograph demonstrating multiple supernumerary teeth in the maxillary and mandibular jaws causing delayed eruption in a patient with neurofibromatosis type 1. The image was obtained from the authors' clinical archive, and written informed consent for publication was obtained from the patient's parents.

In addition, isolated CALMs may occur in otherwise healthy individuals and typically differ from NF1-associated lesions in color, distribution, and border regularity.[7]

Treatment of Neurofibromatosis Type 1

The management of NF1 is primarily symptomatic and supportive, relying on regular clinical surveillance, multidisciplinary care, and individualized long-term follow-up. Surgical intervention remains the mainstay of treatment for symptomatic tumors and skeletal deformities, while systemic therapies are reserved for selected cases.[7,10]

In recent years, targeted therapies acting on the RAS–MAPK signaling pathway, particularly MEK inhibitors such as selumetinib, have demonstrated efficacy in reducing the volume of plexiform neurofibromas and improving associated morbidity.[5] Overall, early diagnosis and coordinated multidisciplinary management are essential to optimize clinical outcomes and enhance quality of life in individuals with NF1.[25,26]

Follow-up in Neurofibromatosis Type 1

Given its multisystem involvement and increased risk of complications, NF1 requires lifelong, multidisciplinary follow-up. Regular clinical evaluations are recommended to facilitate the early detection and management of disease-related manifestations, which is considered more effective than routine laboratory or imaging-based screening alone.[7,11]

Follow-up strategies should be individualized according to clinical severity, with closer surveillance warranted in patients at higher risk of disease progression or malignant transformation.[1]

Noonan Syndrome

Noonan syndrome is one of the most common RASopathies, with an estimated incidence of approximately 1 in 2000-2500 live births, and is caused by pathogenic variants in genes involved in the RAS–MAPK signaling pathway, most frequently *PTPN11*, followed by *RAF1* and *SOS1*.[33-35]

Clinically, NS is characterized by distinctive craniofacial features, congenital heart defects, and postnatal growth retardation, although the facial phenotype may become less pronounced with age. From a dental perspective, oral and craniofacial manifestations are common and may represent early diagnostic clues, particularly in pediatric patients. Frequently reported findings include a high-arched palate, malocclusion, micrognathia, and speech articulation difficulties.[36] Additional dental anomalies such as delayed or ectopic tooth eruption, tooth agenesis, enamel and root defects, increased caries susceptibility, periodontal disease, and jaw lesions resembling cherubism have also been described.[36,37]

Given the marked phenotypic variability and overlap with other RASopathies, recognition of these oral features by pediatric dentists may facilitate earlier suspicion and timely referral, underscoring the role of dental professionals in multidisciplinary care.[34,35]

Noonan Syndrome with Multiple Lentigines (LEOPARD Syndrome)

Noonan syndrome with multiple lentigines (NS-ML), historically referred to as LEOPARD syndrome, is a rare autosomal dominant RASopathy caused by pathogenic variants in *PTPN11*, *RAF1*, or *BRAF*, with *PTPN11* mutations accounting for the majority of cases.[23,33,35] Clinically, NS-ML shares overlapping features with NS but is distinguished by the presence of multiple lentigines and a higher prevalence of sensorineural hearing loss. Cardiac involvement differs from classic NS, as hypertrophic cardiomyopathy is more frequently observed than pulmonary stenosis.[23,33-35]



Figure 3. Intraoral photograph demonstrating delayed eruption of the maxillary central incisors associated with supernumerary teeth in a child with neurofibromatosis type 1. The image was obtained from the authors' clinical archive, and written informed consent for publication was obtained from the patient's parents.

Craniofacial characteristics are generally similar to those seen in NS and may include hypertelorism, mandibular prognathism, macroglossia, and distinctive facial features such as ptosis and a broad nasal bridge. Cutaneous manifestations consist of CALMs and lentigines; the latter typically emerge in early childhood, increase in number until puberty, and predominantly affect the face and upper trunk, while usually sparing the oral mucosa.[20,33,35]

From a dental perspective, oral and craniofacial anomalies have been reported in NS-ML, including agenesis of maxillary lateral incisors and canines, as well as alterations in jaw growth and craniofacial proportions.[36,37] Awareness of these features during routine dental examinations may facilitate early clinical suspicion and appropriate referral, underscoring the role of pediatric dentists within the multidisciplinary management of affected individuals.

Capillary Malformation–Arteriovenous Malformation Syndrome

Capillary malformation–arteriovenous malformation syndrome is a rare autosomal dominant vascular disorder caused by heterozygous loss-of-function mutations in the *RASA1* gene, which encodes p120-RASGAP, a negative regulator of the RAS–MAPK signaling pathway.[3,38-40] The condition is characterized by multifocal capillary malformations that may be associated with high-flow arteriovenous malformations affecting multiple organ systems, most commonly the skin.[38,39] Cutaneous lesions typically present as small pink-to-red macules, sometimes surrounded by a pale halo.

Craniofacial involvement is relatively common in CM–AVM syndrome, particularly affecting the face and neck, and may be associated with soft tissue hypertrophy. Although mucosal involvement is uncommon, lesions may occur along the vermilion border of the lips.[40] Of particular relevance to dental practice, intraosseous arteriovenous malformations of the maxilla or mandible may occur, potentially leading to occlusal discrepancies, increased tooth mobility, and spontaneous or recurrent gingival bleeding.[38,39] These findings may be encountered during routine dental examinations and should raise clinical suspicion.

Visceral arteriovenous malformations, especially intracranial or spinal lesions, are associated with a more severe prognosis and increased morbidity.[38,39] In this context, early recognition of oral and craniofacial vascular abnormalities by dental professionals is critical, as timely referral and multidisciplinary management may reduce the risk of serious complications.

Costello Syndrome

Costello syndrome is a rare autosomal dominant RASopathy caused by activating mutations in the *HRAS* proto-oncogene, resulting in constitutive upregulation of the RAS–MAPK signaling pathway.[41-43] It is a multisystem congenital disorder characterized by distinctive craniofacial features, cardiac abnormalities, dermatologic findings, postnatal growth retardation, and an increased predisposition to benign and malignant tumors, the latter representing the highest cancer risk among RASopathies.[23,41,44]

Craniofacial characteristics in CS are typically coarse and become more pronounced with age. Common features include relative macrocephaly, hypertelorism, downslanting palpebral fissures, epicanthal folds, a short nose with a depressed nasal bridge and broad nasal tip, full cheeks, a wide mouth with thickened lips, and low-set, posteriorly rotated ears.[41,44] These features contribute to a recognizable facial phenotype that distinguishes CS from other RASopathies.

From a dental perspective, oral and dental manifestations are frequent and distinctive in CS. Reported findings include thin and hypomineralized enamel, delayed tooth development and eruption, hypodontia or supernumerary teeth, bifid uvula, gingival hyperplasia, alveolar ridge thickening, high-arched palate, and malocclusion—most commonly Class 3 malocclusion, anterior open bite, and posterior crossbite.[30,36,37] Awareness of this characteristic dental phenotype during pediatric dental assessments may aid early recognition and appropriate referral, particularly given the phenotypic overlap of CS with NS and CFCS in early childhood.[3,23,44]

Cardio-Facio-Cutaneous Syndrome

Cardio-facio-cutaneous syndrome is one of the least common RASopathies, with an estimated incidence of approximately 1 in 810 000 live births.[3,45] The condition is caused by activating mutations most frequently involving *BRAF*, *MAP2K1*, and *MAP2K2*, and less commonly *KRAS*, leading to dysregulation of the RAS–MAPK signaling pathway.[3,46] Cardio-facio-cutaneous syndrome shows clinical overlap with NS and CS but is distinguished by its characteristic ectodermal involvement and a higher prevalence of neurodevelopmental impairment.[44,45]

Clinically, affected individuals often present with congenital cardiac anomalies, short stature, feeding difficulties, growth retardation, and developmental delay. Ectodermal abnormalities are particularly prominent and include sparse, curly, or brittle hair, hyperkeratotic skin, scalp eczema, and in some cases near-total alopecia, features that may facilitate early clinical recognition.[44,45] Craniofacial characteristics typically include relative macrocephaly with a tall cranial vault, bitemporal narrowing, a broad forehead, hypertelorism, a short nose with a flattened nasal bridge and enlarged nasal tip, and low-set, posteriorly rotated ears.[35,45]

From a dental perspective, oral and occlusal anomalies are commonly observed in CFCS. Reported intraoral findings include a high-arched palate, anterior open bite, and posterior crossbite, which may contribute to functional and orthodontic challenges in affected children.[36,37] Recognition of these oral and craniofacial features during pediatric dental examinations may assist in early suspicion and appropriate referral, particularly in the context of overlapping phenotypes among RASopathies.

Legius Syndrome

Legius syndrome is a rare autosomal dominant RASopathy caused by pathogenic variants in the *SPRED1* gene, which encodes a negative regulator of the RAS–MAPK signaling pathway.[32] Although its exact prevalence is unknown, LS is considered uncommon, with fewer than 300 molecularly confirmed cases reported to date.[47] Clinically, LS is often described as an NF1-like condition, as affected individuals typically present with multiple CALMs and intertriginous freckling; however, neurofibromas, iris Lisch nodules, and central nervous system tumors are characteristically absent, distinguishing LS from NF1.[32,47]

Craniofacial features in LS may overlap with those observed in other RASopathies, particularly NS, and can include relative or absolute macrocephaly, ocular hypertelorism, and thoracic wall anomalies such as pectus excavatum.[32,36,45,47] From a dental perspective, oral manifestations in LS appear to be limited, and the absence of NF1-associated oral tumors or jaw lesions may serve as an important diagnostic clue in the differential diagnosis of children presenting with multiple CALMs. Recognition of this pattern by pediatric dentists may help avoid misclassification as NF1 and support appropriate genetic referral.

Discussion

RASopathies comprise a heterogeneous group of developmental disorders characterized by dysregulation of the RAS–MAPK

signaling pathway, resulting in marked phenotypic variability and substantial clinical overlap. Despite advances in molecular genetics and improved genotype–phenotype correlations, early diagnosis remains challenging, particularly in childhood, when systemic manifestations may be subtle or incomplete.

In this context, oral, dental, and craniofacial manifestations represent underrecognized yet clinically meaningful diagnostic clues. Many of these findings—such as malocclusion patterns, delayed tooth eruption, jaw anomalies, gingival alterations, or vascular lesions—may be encountered during routine pediatric dental examinations. Their identification can therefore play a pivotal role in raising early clinical suspicion and prompting timely genetic referral, especially in syndromes where oral findings precede or parallel systemic features.

Importantly, the nature and frequency of oral manifestations vary across different RASopathies. Findings observed in NF1, such as gingival enlargement, pigmentation, delayed eruption, and jaw anomalies, exemplify how these manifestations may serve as accessible and early indicators of underlying RAS–MAPK dysregulation. While conditions such as CS, CFCS, and NS frequently present with distinctive dental and craniofacial phenotypes, others—such as LS—are characterized by the relative absence of oral tumors or jaw involvement, which may aid in the differential diagnosis from NF1. These distinctions underscore the value of oral findings for both early recognition and diagnostic refinement within the RASopathy spectrum (Table 1). The oral and craniofacial findings summarized in Table 1 illustrate the heterogeneity of RASopathies and highlight features that may assist clinicians in differentiating between syndromes during routine dental assessment.

At the biological level, dysregulation of the RAS–MAPK pathway affects cellular proliferation, differentiation, and tissue development,

Table 1. Oral, Dental, and Craniofacial Manifestations in RASopathies

RASopathies	Gingival and Oral Soft Tissue Findings	Dental and Occlusal Manifestations	Skeletal and Craniofacial Manifestations
Neurofibromatosis type 1 (NF1)	Periodontitis, gingival enlargement (frequently reported), melanin pigmentation, oral/perioral neurofibromas, plexiform neurofibromas Tongue involvement: neurofibromas, macroglossia, and enlarged fungiform papillae	Dental caries, tooth agenesis, supernumerary teeth (occasionally reported), impacted teeth malposition, diastema class 3 molar relationships	Enlargement of the alveolar process, widened mandibular foramen, enlargement of coronoid and sigmoid notches, concavity on posterior mandibular border
Noonan syndrome (NS)	Periodontal disease	Dental caries, dental erosion, ectopic eruption, delayed eruption, impacted teeth, tooth agenesis, root and enamel anomalies, malocclusion (frequently reported), articulation difficulties	High-arched palate (commonly reported), micrognathia (frequently reported), mandibular cysts resembling cherubism, giant cell lesions
Noonan syndrome with multiple lentigines (NS-ML/LEOPARD)	Not consistently reported	Agenesis of maxillary lateral incisors and canines	Not consistently reported
Capillary malformation–arteriovenous malformation (CM–AVM) syndrome	Gingival bleeding (secondary to vascular involvement)	Tooth mobility (secondary to AVM)	Intraosseous AVMs of the maxilla and mandible, resulting in occlusal discrepancies
Costello syndrome (CS)	Gingival hyperplasia (frequently reported)	Thin and hypomineralized enamel (occasionally reported), delayed tooth development and eruption, hypodontia or supernumerary teeth, anterior open bite, posterior crossbite, malocclusion (frequently reported)	Thickening of the alveolar ridge, high-arched palate
Cardio-facio-cutaneous syndrome	Not consistently reported	Anterior open bite (frequently reported), posterior crossbite	High-arched palate (commonly reported)
Legius syndrome	Not consistently reported	Not consistently reported	Not consistently reported

CFC, cardio-facio-cutaneous syndrome; CM–AVM, capillary malformation–arteriovenous malformation syndrome; CS, Costello syndrome; NF1, neurofibromatosis type 1; NS, Noonan syndrome; NS-ML, Noonan syndrome with multiple lentigines.
Manifestations listed are those most frequently reported in the literature and may vary in prevalence among individuals with the same syndrome. The term "not consistently reported" reflects the currently available literature rather than the definite absence of manifestations.
This table summarizes the major gingival, dental, and craniofacial manifestations associated with RASopathies. The findings are organized by syndrome and subdivided into 3 main categories: gingival and oral soft tissue findings, dental and occlusal manifestations, and skeletal and craniofacial features. Data were compiled and synthesized from previously published studies.[10,30,31,36-40]

providing a plausible mechanistic explanation for the craniofacial growth disturbances, dental anomalies, and soft-tissue alterations observed in these conditions. Linking molecular mechanisms with clinical oral phenotypes may therefore enhance diagnostic accuracy and support more individualized patient management.

From a management perspective, current therapeutic strategies for RASopathies remain largely supportive and multidisciplinary, focusing on surveillance and treatment of disease-related complications. Emerging targeted therapies, particularly inhibitors of the RAS–MAPK pathway, hold promise for modifying disease course in selected conditions; however, evidence regarding their long-term efficacy and safety is still evolving. In this setting, early diagnosis facilitated by oral findings may optimize the timing of intervention and longitudinal care planning.

Several limitations within the existing literature should be acknowledged. Much of the available evidence regarding oral and craniofacial manifestations is derived from small case series or heterogeneous cohorts that include both pediatric and adult patients, which may limit precise prevalence estimates and age-specific interpretation. These limitations emphasize the need for prospective, pediatric-focused studies with standardized reporting of dental and craniofacial manifestations. Strengthening collaboration between pediatric dentists, geneticists, and medical specialists will be essential for improving early recognition and comprehensive care of children with suspected RASopathies.

Conclusion

In summary, early clinical recognition of RASopathies remains challenging despite significant advances in molecular genetics. Oral and craniofacial manifestations may serve as valuable early diagnostic indicators, sometimes preceding systemic features, particularly in pediatric patients. Increased awareness of these findings among pediatric dentists and dental specialists may facilitate earlier suspicion, timely genetic referral, and improved multidisciplinary care.

Continued progress in genetic diagnostics and targeted therapies is expected to further refine the management of RASopathies. However, integrating dental assessment into the routine evaluation of children with suspected syndromic features remains essential for achieving timely diagnosis, effective long-term monitoring, and improved patient outcomes.

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