Turkish Journal of Pediatric Disease

Review Article

RAS/MAPK Pathway and RASopathies

Aslı Genç, Esra Kılıç

Department of Pediatric Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye

Corresponding Author: **Aslı Genç** e-mail: asligenc92@gmail.com

Received : 10.01.2026, Accepted : 25.04.2026 DOI: 10.12956/TJPD.2025.1329

ABSTRACT

The RAS/Mitogen-Activated Protein Kinase (MAPK) pathway is a core developmental signaling cascade that regulates proliferation, differentiation, survival, and tissue growth across multiple organ systems. Germline dysregulation of this pathway results in RASopathies. Although the causal variants affect different components of the pathway, they converge on abnormal downstream signaling. This explains why these disorders share a recognizable clinical core despite clear syndrome-specific differences. The most prevalent and well-known entity is Noonan syndrome, while other major subtypes include cardiofaciocutaneous syndrome, Costello syndrome, and Noonan syndrome with multiple lentigines.

RASopathies are characterized by distinctive craniofacial features and multisystem involvement. Congenital heart disease is a significant cause of morbidity. Neurodevelopmental difficulties are common across the spectrum and may be particularly pronounced in Cardiofaciocutaneous and Costello syndromes. Short stature, pectus anomalies, scoliosis, and other musculoskeletal findings are also recurrent features. Another important concern is the malignancy risk, which varies significantly by genotype.

Although these disorders share a common pathway, genotype-phenotype correlations are increasingly relevant in daily practice. Molecular findings now directly inform risk assessment and long-term follow-up. In parallel, early experience with pathway-directed therapies is beginning to influence the management of selected complications. MEK inhibitors have shown promising results in selected manifestations, particularly hypertrophic cardiomyopathy and refractory lymphatic complications.

In this review, we discuss the biological organization of the RAS/MAPK pathway and relate it to the clinical spectrum of RASopathies. We focus on shared and distinguishing phenotypic features, clinically relevant genotype-phenotype correlations, and the emerging role of targeted therapies.

Keywords: Genotype-Phenotype Correlation, Noonan syndrome, MAP Kinase Signaling System, RASopathies

Introduction

The RAS/MAPK pathway mediates the transmission of extracellular signals into intracellular responses that control key developmental processes. It regulates cell proliferation, differentiation, survival, and tissue growth across multiple organ systems. Precise regulation of this signaling is required for normal development and maintenance of tissue homeostasis (1–4).

The canonical pathway begins when cell surface receptors trigger RAS, initiating the RAF-MEK-ERK kinase cascade (Figure 1). ERK acts as the main downstream effector and phosphorylates multiple targets, which influences gene expression and cellular behavior (2,3,5). Cycling between active and inactive states, RAS proteins function as the pathway's molecular switches. This cycle is regulated by guanine nucleotide exchange factors and GTPase-activating proteins, which promote RAS activation and signal termination, respectively (1) (Figure 2). Efficient signaling relies on spatial organization at cellular membranes, where RAS and its regulators assemble with downstream effectors. This organization helps determine signaling specificity rather than simple pathway activation (1,3). Feedback mechanisms, phosphatases, and scaffold proteins further restrain signal strength and duration. Without these regulatory layers, identical stimuli could produce very different biological outcomes (2,3,6). Moreover, RAS/MAPK signaling is dynamic rather than static. Differences in the magnitude, duration, and timing of ERK activation can lead to distinct biological outcomes, even within the same cell type (2,5).

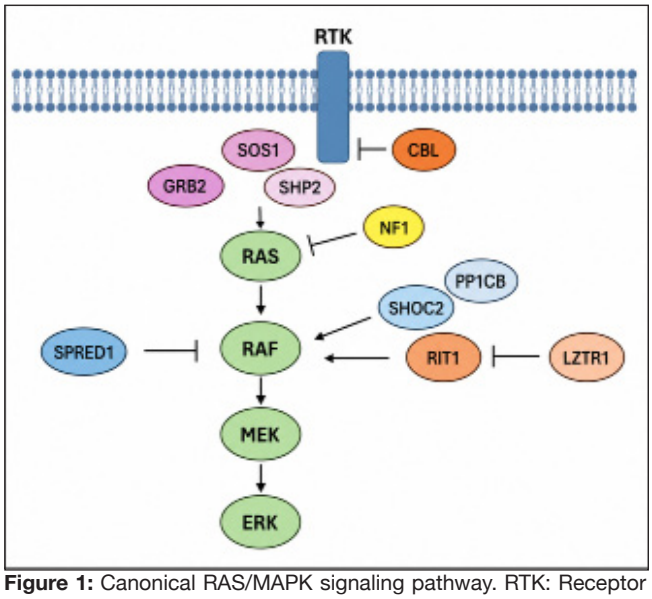

Figure 1: Canonical RAS/MAPK signaling pathway. RTK: Receptor Tyrosine Kinase

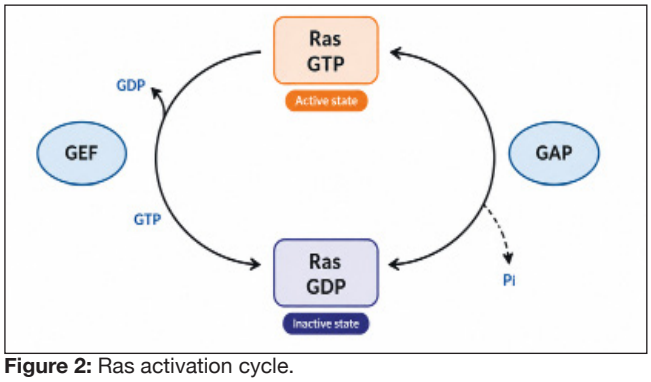

Figure 2: Ras activation cycle.

Accessory proteins contribute to the spatial and temporal organization of signaling components. Proteins such as scaffolds, adaptors, and other modulators, including SPRED1, SHOC2, and *CBL*, enable fine-tuning of RAS/MAPK signaling rather than simple on-off activation (Figure 1). They support graded and context-dependent responses during development and across different tissues (1,6). Disruption of the RAS/MAPK pathway changes normal developmental signaling and provides the molecular basis for a group of genetic disorders caused by germline pathway dysregulation (4,7).

RASopathies are a group of disorders that share overlapping features caused by germline pathogenic variants in genes that encode components or regulators of the RAS/MAPK pathway. These variants can affect different parts of the pathway, including upstream activators, core signaling proteins, or regulatory factors. These disorders are caused by dysregulated RAS/MAPK signaling, although the molecular consequences vary according to the affected gene and variant. Because the primary defect reflects dysregulated signaling rather than a single-gene effect, RASopathies are better viewed within a pathway-based framework (4,7,8). This perspective also provides a rationale for therapies that aim to modulate pathway activity (4).

RASopathies include Noonan syndrome (NS, MIM #163950), Cardiofaciocutaneous syndrome (CFCS, MIM #115150), Costello syndrome (CS, MIM #218040), Legius syndrome (LS, MIM #611431), Neurofibromatosis–Noonan syndrome (NF-NS, MIM #613113), Noonan syndrome with loose anagen hair (NS/LAH, MIM #607721), Noonan syndrome with multiple lentigines (NSML, previously LEOPARD syndrome, MIM #151100), Neurofibromatosis type 1 (*NF1*, MIM #162200), and several rarer related disorders (Table I). Clinically, these disorders are often discussed as core syndromic forms, neurocutaneous conditions, and less common related entities. This classification helps organize a phenotypically broad but mechanistically related group of conditions within the RAS/MAPK pathway spectrum (7,9). Although these disorders share overlapping clinical features, they arise from distinct molecular mechanisms affecting different parts of the pathway. Many disease-associated variants are missense changes that alter pathway output, often by increasing or prolonging signaling, particularly at the level of ERK activation. In contrast, loss-of-function mechanisms are central in specific conditions such as *NF1* and SPRED1-related disease. Variants in the same gene can lead to different clinical phenotypes depending on their type and functional impact within the pathway. This allelic heterogeneity explains both the overlap and the variable expressivity within individual syndromes, supporting a pathway-based classification rather than a strict one gene-one disease model (8,10,11).

In the following sections, we relate core RAS/MAPK biology to the clinical presentation of the major RASopathies, with particular emphasis on the syndromic forms most relevant to pediatric practice. We also review emerging pathway-directed treatments and consider their practical implications for long-term care.

Noonan Syndrome (NS)

As the most common RASopathy, Noonan syndrome (NS) is often considered the clinical prototype of this group (4,9). It is typically characterized by a recognizable facial appearance, short stature, and congenital heart disease, although expression is highly variable between individuals (10,12). Its estimated incidence is approximately 1 in 1 000-2 500 live births (8). Somatic oncogenic RAS pathway variants often drive strong and poorly controlled signaling. In contrast, germline variants associated with NS usually produce a milder but persistent disturbance of developmental signaling. This allows embryonic viability, but disrupts normal morphogenesis and tissue differentiation (7,10,13).

The genes most commonly associated with NS are summarized in Table I. Although they affect different nodes of the pathway, they converge on abnormal ERK signaling. Variants in *PTPN11* increase SHP2 activity and enhance RAS/MAPK pathway signaling (11). Building on this mechanism, gain-of-function variants in *SOS1* and *SOS2* promote RAS activation by increasing the amount of its active, GTP-bound form. Pathogenic variants in downstream signaling proteins such as *RAF1*, and less commonly *BRAF*, enhance signal propagation through the MEK–ERK cascade, whereas variants in RAS-family genes, including *KRAS*, *NRAS*, and *RIT1*, dysregulate upstream pathway activation through gene-specific mechanisms (7,13,14). Experimental data suggest that even modest increases in

Table I: Molecular mechanisms and key clinical domains of RASopathies

Disorder	Primary Pathway Node	Gene(s)	Molecular Mechanism	Typical Variant Effect	Key Clinical Domains	Therapeutic Implications
Noonan syndrome (NS)	Upstream signal transduction / pathway regulation	*PTPN11, SOS1, SOS2, RAF1, RIT1, KRAS, BRAF, LZTR1, NRAS, RRAS2, RASA2, SPRED2*	Abnormal upstream pathway activation or signal amplification	Predominantly gain-of-function or dysregulated activation	Craniofacial features, short stature, cardiac, and neurodevelopmental involvement	Potential responsiveness to pathway-modulating therapies; emerging interest in MEK inhibition and upstream signal modulation
Cardiofaciocutaneous syndrome (CFCS)	Core kinase cascade (RAF–MEK–ERK)	*BRAF, MAP2K1, MAP2K2, KRAS*	Constitutive activation of the RAF–MEK–ERK cascade	Gain-of-function	Severe neurodevelopmental impairment, epilepsy, characteristic ectodermal features, cardiac defects, growth failure	Strong rationale for downstream pathway inhibition; MEK inhibitors explored in severe or refractory cases
Costello syndrome (CS)	RAS activation	*HRAS*	Persistent HRAS activation due to impaired GTP hydrolysis	Gain-of-function	Failure to thrive, cardiomyopathy, characteristic ectodermal features, severe neurodevelopmental impairment, increased malignancy risk	Potential benefit from pathway modulation; careful balance required due to tumor predisposition
Neurofibromatosis type 1 (NF1)	Negative regulation of RAS	*NF1*	Loss of neurofibromin-mediated RAS-GAP activity resulting in increased RAS signaling	Loss-of-function	Cafe-au-lait macules, Lisch nodules, skeletal abnormalities, tumor predisposition	Established clinical use of MEK inhibitors for plexiform neurofibromas
Legius syndrome (LS)	Negative regulation of RAS	*SPRED1*	Impaired recruitment of neurofibromin to the membrane, leading to increased RAS/MAPK signaling	Loss-of-function	Café-au-lait macules, absence of tumor burden	Supportive management; emphasizes need for molecular distinction from NF1 to avoid unnecessary tumor surveillance
Noonan syndrome with multiple lentigines (NSML)	Signal modulation at SHP2 / RAF level	*PTPN11, RAF1, BRAF*	Altered phosphatase or kinase activity with paradoxical effects on downstream signaling	Dominant-negative or dysregulated signaling	Multiple lentigines, hypertrophic cardiomyopathy, growth delay, sensorineural hearing loss	Potential responsiveness to pathway modulation; cardiac phenotype guides surveillance and therapy
Noonan syndrome with loose anagen hair (NS/LAH)	Pathway scaffolding and signal flux control	*SHOC2, PPP1CB*	Aberrant pathway scaffolding causing increased and mislocalized MAPK signaling	Gain-of-function	Distinct hair anomalies, developmental delay, cardiac defects, growth failure	Highlights role of non-enzymatic regulators; supports upstream signal modulation strategies
CBL syndrome	Ubiquitin-mediated signal termination	*CBL*	Impaired ubiquitination and degradation of activated signaling complexes	Loss-of-function / dominant-negative	Developmental delay, immune dysregulation, predisposition to JMML-like myeloproliferation	Clinical focus on hematologic surveillance; pathway inhibition considered in selected proliferative phenotypes

ERK signaling can disturb developmental processes such as cell fate decisions and tissue patterning. This sensitivity may partly explain the multisystem involvement observed in NS (2,5,13).

The craniofacial phenotype of NS commonly includes hypertelorism, downslanting palpebral fissures, ptosis, low-set posteriorly rotated ears, and a broad or webbed neck. In infancy, these features may be subtle, becoming easier to recognize during early childhood. Growth retardation is common, with postnatal growth failure being more prominent than prenatal growth restriction. Many children present with feeding difficulties and failure to thrive in infancy, contributing to early growth impairment (12,15). Clinical diagnosis of NS is supported by diagnostic scoring systems that integrate facial features, cardiac defects, growth patterns, and family history (16) (Table II). With the widespread use of molecular testing, genetic confirmation has become central to diagnosis, particularly in individuals with atypical or mild phenotypes (12,17). Prenatal diagnosis is increasingly recognized

Table II: Van der Burgt diagnostic criteria in NS, adapted from Van der Burgt (16).

Major Findings	Minor Findings
Typical facial dysmorphology (ptosis, downslanting palpebral fissures, low-set, posteriorly rotated ears, etc.)	Suggestive face dysmorphology
PS, HCM, and/or ECG typical of NS	Other cardiac defects
Height below the 3rd centile	Height below 10th centile
Pectus deformity	Broad thorax
First-degree relative with definite NS	First-degree relative with suggestive NS
Intellectual disability, cryptorchidism, and lymphatic dysplasia	One of the intellectual disability, cryptorchidism, or lymphatic dysplasia

Patients are diagnosed with NS if they have either one major facial feature plus one additional major criterion or two minor criteria, or a minor facial feature plus two major criteria or three minor criteria. ***NS:*** *Noonan syndrome,* ***HCM:*** *Hypertrophic cardiomyopathy,* ***ECG:*** *Electrocardiogram*

Table III: Well-recognized genotype-phenotype correlations reported in Noonan syndrome

Gene	Approximate frequency in NS	Pathway effect	Characteristic clinical associations
PTPN11	40–50%	Increased SHP2 phosphatase activity leading to enhanced RAS/MAPK signaling	PS, short stature, variable developmental delay
SOS1	10–15%	Enhanced RAS activation through increased guanine nucleotide exchange activity	Prominent ectodermal findings (e.g., keratosis pilaris, sparse hair), typically normal or mild cognitive involvement
RAF1	5–10%	Increased downstream MAPK signaling due to impaired inhibitory phosphorylation	Strong association with HCM
RIT1	5%	Dysregulated RAS-like signaling affecting downstream pathway activation	HCM, lymphatic abnormalities, prenatal findings
KRAS	<5%	Increased RAS signaling due to impaired GTPase cycling	More severe developmental delay and complex phenotype
LZTR1	~5–10%	Impaired ubiquitination and regulation of RAS proteins	PS and typical Noonan features with variable developmental delay; both dominant and recessive inheritance described

NS: *Noonan syndrome,* ***PS:*** *Pulmonary valve stenosis,* ***HCM:*** *Hypertrophic cardiomyopathy. Frequencies are approximate and may vary across cohorts and sequencing strategies.*

through characteristic ultrasound findings, especially in the presence of lymphatic abnormalities or congenital heart disease, prompting targeted genetic evaluation (18). Well-recognized genotype-phenotype correlations reported in NS are summarized in (Table III).

Short stature is a common clinical feature. Bone age delay is frequent, and growth velocity may decline during childhood. Skeletal involvement also includes pectus deformities, scoliosis or kyphosis, limb abnormalities, and reduced bone mineral density (15,19).

Cardiac disease remains one of the most important determinants of morbidity in NS. While pulmonary valve stenosis (PS) and hypertrophic cardiomyopathy (HCM) are common, atrial septal defects and complex structural lesions can also be observed. Cardiac manifestations may present prenatally, at birth, or later in childhood. The disease severity ranges from mild lesions requiring observation to progressive conditions needing medical or surgical intervention (12,20). Specific genotype-phenotype correlations have been established for cardiac involvement: gain-of-function variants in *RAF1* show a strong association with HCM, reflecting enhanced MAPK signaling due to impaired inhibitory phosphorylation of the protein (21,22) (Table III). Pathogenic variants in *RIT1* are likewise frequently associated with severe and early-onset cardiac phenotypes, including HCM and PS (14,20). This genotype–cardiac association is clinically important, as MEK inhibition with trametinib has shown benefit in selected patients with severe disease (23,24).

Lymphatic abnormalities are an important but often underrecognized feature of NS. They may already be apparent prenatally, presenting as increased nuchal translucency, cystic hygroma, pleural effusions, or hydrops fetalis. After birth, peripheral lymphedema, chylothorax, or intestinal lymphangiectasia may occur. These complications may be transient or persistent and can significantly contribute to morbidity, particularly in infancy and early childhood (18,25).

Neurodevelopmental manifestations are core features of NS rather than secondary complications. Although overall intellectual functioning often falls within the low-normal range, affected children have a higher prevalence of neurodevelopmental disorders compared with the general population (26,27). Attention-deficit/hyperactivity disorder (ADHD) appears to be the most common condition, while oppositional defiant disorder and autism spectrum traits are also frequently reported (26). A systematic review and meta-analysis confirmed an increased prevalence of neurodevelopmental and psychiatric conditions in NS, including intellectual developmental disorder, ADHD, autism spectrum disorder, epilepsy, and anxiety or depressive symptoms (27).

Children with NS have an increased malignancy risk compared with the general pediatric population, reflecting germline RAS/MAPK dysregulation. Cohort studies estimate an approximately eightfold relative increase, although the absolute risk remains moderate (28). Reported tumors include juvenile myelomonocytic leukemia

(JMML), other myeloproliferative conditions, acute leukemias, rhabdomyosarcoma, neuroblastoma, and low-grade gliomas. Despite this increased risk, routine universal cancer surveillance is not recommended; instead, careful clinical monitoring is advised (28).

Classical growth hormone (GH) deficiency is not consistently present in NS, and growth impairment may partly reflect altered RAS/MAPK pathway signaling. GH, treatment generally improves growth velocity and height standard deviation score, although response may vary according to age at treatment initiation and genotype, particularly in individuals with *PTPN11*-related disease (12,29). Current evidence suggests that therapy is usually well tolerated, including in many patients with congenital heart disease, provided that cardiovascular and oncologic monitoring is maintained (12,28,29). Overall, GH remains a reasonable option for selected children with NS when used within a structured follow-up plan.

Cardiofaciocutaneous syndrome (CFCS)

Cardiofaciocutaneous syndrome (CFCS) stands out as a rare RASopathy defined by multisystem involvement, most notably significant developmental delay and ectodermal abnormalities (30,31). A nationwide epidemiologic survey suggested a prevalence of approximately 1 in 800 000 live births, although precise epidemiologic data remain limited (31-33). While *BRAF* variants are the most frequent cause, pathogenic changes in *MAP2K1*, *MAP2K2*, or *KRAS* also drive the pathway dysregulation that disrupts normal tissue maturation (30,34) (Table I). These alterations dysregulate ERK signaling during development and thereby affect proliferation, differentiation, and tissue maturation (34).

Cardiac findings commonly include PS, septal defects, and HCM, with variable severity requiring individualized follow-up (9,30). Craniofacial findings typically include a high forehead with bitemporal narrowing, hypertelorism, downslanting palpebral fissures, low-set ears, and a short nose with a depressed bridge (9,30,31). Diagnostic clues are often found in the skin and hair; hyperkeratosis and sparse, curly hair are hallmarks that support the clinical diagnosis across diverse populations. A multicenter dermatologic study reported common features such as hyperkeratosis, keratosis pilaris, sparse or curly hair, ulerythema ophryogenes, and palmoplantar keratoderma (35). Similar clinical patterns have been described in molecularly confirmed cohorts from different populations, supporting the consistency of the CFCS phenotype (33).

Feeding difficulties are highly prevalent in infancy and often contribute to failure to thrive. Severe reflux, vomiting, oral feeding difficulty, and the need for nutritional support are common in infancy. Musculoskeletal involvement is also common and includes pectus deformities, scoliosis or kyphosis, joint laxity, and other skeletal anomalies (30,33).

Neurologic involvement represents one of the most prominent clinical aspects of CFCS. In a multinational cohort of 138 individuals, intellectual disability was present in 82% and seizures in 55% of patients (36). Seizure onset most commonly occurred in early or middle childhood. Genotype-specific patterns have also been described: variants in *BRAF* and *MAP2K1* are generally associated with a higher frequency and greater severity of seizures compared with *MAP2K2* variants (36). Studies focusing on *BRAF*-related disease have reported particularly high rates of refractory and polymorphic seizure types (37). In addition to epilepsy, affected individuals frequently exhibit motor delay, hypotonia, and sleep disturbances, further emphasizing the significant neurologic burden associated with CFCS (33). CFCS may also include immune involvement. In an international cohort, a substantial subset of patients exhibited increased infection susceptibility and lymphopenia, highlighting the need for broader clinical awareness (38).

Costello Syndrome (CS)

Among the RASopathies, CS has a particularly recognizable clinical profile, primarily defined by its multisystem involvement and a significant predisposition to malignancy (39,40). CS is caused by heterozygous gain-of-function germline variants in *HRAS*, most commonly missense substitutions affecting codons 12 or 13. These mutations impair normal GTP hydrolysis in *HRAS* protein, resulting in persistent activation of RAS/MAPK cascade (39). Infants typically present with coarse facial features, macrocephaly, and severe feeding difficulties. However, the most striking diagnostic clues are often ectodermal; redundant skin, deep palmar and plantar creases, and cutaneous papillomas are hallmarks that help clinicians differentiate CS from other disorders in the RASopathy spectrum. CS also carries a well-recognized predisposition to both benign and malignant tumors, particularly rhabdomyosarcoma, neuroblastoma, and transitional cell carcinoma of the bladder (39,40).

Dermatologic findings are prominent in CS and may provide useful diagnostic clues. A prospective multicenter study reported frequent features, including curly or sparse hair, prominent eyebrows, acral excess skin with deep palmoplantar creases, papillomas or keratotic papules, acanthosis nigricans, and palmoplantar hyperkeratosis. These dermatologic findings may provide useful clues when distinguishing CS from other RASopathies (41).

Musculoskeletal abnormalities are also common in CS and include progressive spinal deformities, particularly kyphosis and scoliosis, which may develop during childhood and require longitudinal monitoring (42). Ophthalmologic abnormalities are frequently reported as well. These may include refractive errors, strabismus, nystagmus, and ptosis, while optic nerve and retinal abnormalities have also been described (43). Together, these observations support regular ophthalmologic assessment in individuals with CS (43,44).

One of the features that makes CS especially important in long-term follow-up is its marked tumor predisposition. A systematic review and meta-analysis demonstrated a markedly increased risk of malignancy compared with the general population. Tumors most often arise during childhood, although risk persists into adolescence and adulthood (45). Because of this elevated risk, children with CS require structured longitudinal follow-up and age-appropriate tumor surveillance. Current consensus guidelines

emphasize multidisciplinary follow-up and risk-adapted surveillance to facilitate early tumor detection (28).

CFCS and CS share substantial phenotypic overlap. Several features are more typically associated with CS, including deep palmar and plantar creases, joint hyperextension, and hyperpigmentation. These findings may also occur in CFCS, but are generally less prominent, reflecting the clinical overlap between the two disorders (46). In clinical practice, these distinctions may help differentiate the two disorders despite their shared pathway biology.

Noonan syndrome with multiple lentigines (NSML)

Noonan syndrome with multiple lentigines (NSML), historically referred to as LEOPARD syndrome, is a rare RASopathy characterized by multiple lentigines together with cardiac, facial, and growth abnormalities. The acronym "LEOPARD" reflects the key clinical features: lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, genital anomalies, growth retardation, and deafness. The estimated prevalence is approximately 1 in 100 000 individuals. Most cases are associated with pathogenic variants in *PTPN11*, although variants in *RAF1* and, rarely, *BRAF* have also been reported (Table I). Unlike classic NS, where variants typically increase pathway signaling, NSML-associated *PTPN11* variants often impair SHP2 catalytic activity yet still lead to dysregulated downstream signaling in a context-dependent manner (9,47).

Clinically, NSML shows a multisystem phenotype that overlaps with other RASopathies but has several distinguishing features. Lentigines usually become apparent in early childhood and increase in number over time (47). Cardiovascular involvement is common, with HCM representing the most frequent and clinically significant cardiac manifestation. It often develops during childhood and requires longitudinal follow-up (48). Conduction abnormalities and additional structural heart defects may also be observed. Sensorineural hearing loss has been reported in a subset of patients and may occasionally present early, particularly in individuals with *PTPN11*-associated disease (49).

Noonan syndrome with loose anagen hair (NS/LAH)

NS/LAH is a rare RASopathy that shares many clinical features with NS but is distinguished by characteristic hair abnormalities. The disorder is most commonly associated with pathogenic variants affecting the *SHOC2–MRAS–PPP1CB* signaling complex, which modulates RAS/MAPK pathway activation (Figure 1) (9). Individuals typically present with a Noonan-like facial gestalt, postnatal growth retardation, macrocephaly, and variable neurodevelopmental delay. A defining feature is the loose anagen hair phenotype, characterized by sparse, slow-growing, easily pluckable hair reflecting abnormal hair anchoring. Cardiac anomalies may also occur, although the spectrum is variable, and additional findings may become more evident over time (50,51). Recent reports also indicate that recurrent de novo missense variants in *PPP1CB* can produce a closely related phenotype overlapping with NS/LAH, further supporting the role of this signaling complex in disease pathogenesis (52).

Therapeutic Approaches in RASopathies

Management of RASopathies has traditionally focused on symptomatic and multidisciplinary care, addressing cardiac disease, growth problems, neurodevelopmental issues, and other complications (9,53). As understanding of RAS/MAPK pathway biology has improved, interest in therapies targeting this signaling cascade has increased (23).

MEK inhibitors such as trametinib have emerged as a potential targeted approach. Early clinical reports suggest improvement in manifestations related to signaling hyperactivation. Improvement of HCM has been reported in children with RASopathy-associated cardiac disease treated with MEK inhibitors (54). Similar strategies have also been explored in mosaic RASopathies; treatment with a MEK inhibitor in a pediatric patient with *KRAS*-associated epidermal nevus syndrome resulted in clinical benefit (55). In addition, MEK inhibition has been reported to reduce seizure burden in patients with drug-resistant epilepsy associated with CFCS and mosaic *KRAS*-related RASopathies (56). Targeted treatment approaches have also been described for specific complications. In NS, trametinib has been used for severe lymphatic manifestations with reported clinical improvement (24). In NSML, mTOR inhibition with everolimus has been reported as a therapeutic option for severe cardiac involvement in infancy (57).

Advances in targeted oncology have further informed treatment strategies in RAS pathway disorders. Selumetinib represents one of the clearest clinical examples of MAPK pathway inhibition in practice (58). It is approved for symptomatic, inoperable plexiform neurofibromas in children with *NF1*. It has demonstrated meaningful tumor shrinkage together with functional improvements such as reduced pain and improved pulmonary and motor function. MEK inhibitors have also been explored in other *NF1* manifestations, including low-grade gliomas and atypical neurofibromas, although evidence remains limited. Potential benefits for pain and neurocognitive outcomes have also been reported, supporting further investigation of selumetinib in RAS pathway-related conditions (59). Pathway-directed therapies have additionally been explored in RASopathies with skeletal involvement. In osteofibrous dysplasia, preclinical data and a reported case of persistent pseudarthrosis demonstrated improved bone healing following MEK inhibition (60). Although the available experience remains limited, these reports suggest that pathway-directed therapies may benefit selected patients by partially correcting the underlying signaling dysregulation.

Conclusion

RASopathies require careful and long-term clinical follow-up because of their overlapping features and multisystem involvement. Long-term follow-up is particularly important for monitoring potentially life-threatening manifestations such as cardiac disease, while supportive management addressing feeding difficulties and neurodevelopmental challenges plays a critical role in improving patient outcomes. Pathway-directed treatment remains investigational for most RASopathies. However, early reports suggest that selected complications may become amenable to targeted therapy. Most available data come from case reports and small series, and further studies will

be necessary to clarify long-term efficacy and safety in patients with RASopathies. As molecular understanding improves, pathway-directed treatments remain investigational for most RASopathies and have not yet become part of routine clinical care.

References

1. Simanshu DK, Nissley DV, McCormick F. RAS Proteins and Their Regulators in Human Disease. Cell. 2017;170(1):17-33. https://doi.org/10.1016/j.cell.2017.06.009
2. Ram A, Murphy D, DeCuzzi N, et al. A guide to ERK dynamics, part 1: mechanisms and models. Biochem J. 2023;480(23):1887-907. https://doi.org/10.1042/BCJ20230276
3. Martin-Vega A, Cobb MH. Navigating the ERK1/2 MAPK Cascade. Biomolecules. 2023;13(10):1555. https://doi.org/10.3390/biom13101555
4. Hebron KE, Hernandez ER, Yohe ME. The RASopathies: from pathogenetics to therapeutics. Dis Model Mech. 2022;15(2):dmm049107. https://doi.org/10.1242/dmm.049107
5. Ram A, Murphy D, DeCuzzi N, et al. A guide to ERK dynamics, part 2: downstream decoding. Biochem J. 2023;480(23):1909-28. https://doi.org/10.1042/BCJ20230277
6. Pudewell S, Wittich C, Kazemein Jasemi NS, Bazgir F, Ahmadian MR. Accessory proteins of the RAS-MAPK pathway: moving from the side line to the front line. Commun Biol. 2021;4(1):696. https://doi.org/10.1038/s42003-021-02149-3
7. Rauen KA. Defining RASopathy. Dis Model Mech. 2022;15(2):dmm049344. https://doi.org/10.1242/dmm.049344
8. Tidyman WE, Rauen KA. The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev. 2009;19(3):230-6. https://doi.org/10.1016/j.gde.2009.04.001
9. Zenker M. Clinical overview on RASOPATHİES. American J of Med Genetics Pt C. 2022;190(4):414-24. https://doi.org/10.1002/ajmg.c.32015
10. Rauen KA. The RASopathies. Annu Rev Genom Hum Genet. 2013;14(1):355-69. https://doi.org/10.1146/annurev-genom-091212-153523
11. Tartaglia M, Zampino G, Gelb BD. Noonan Syndrome: Clinical Aspects and Molecular Pathogenesis. Mol Syndromol. 2010;1(1):2-26. https://doi.org/10.1159/000276766
12. Reynolds G, Gazzin A, Carli D, et al. Update on the Clinical and Molecular Characterization of Noonan Syndrome and Other RASopathies: A Retrospective Study and Systematic Review. IJMS. 2025;26(8):3515. https://doi.org/10.3390/ijms26083515
13. Tidyman WE, Rauen KA. Pathogenetics of the RASopathies. Hum Mol Genet 2016;25(R2):R123-R132. https://doi.org/10.1093/hmg/ddw191
14. Aoki Y, Niihori T, Banjo T, et al. Gain-of-Function Mutations in *RIT1* Cause Noonan Syndrome, a RAS/MAPK Pathway Syndrome. Am J Hum Genet 2013;93(1):173-80. https://doi.org/10.1016/j.ajhg.2013.05.021
15. Noonan Syndrome Guideline Development Group. Management of Noonan Syndrome: A Clinical Guide. 2010.
16. Van Der Burgt I. Noonan syndrome. Orphanet J Rare Dis. 2007;2(1):4. https://doi.org/10.1186/1750-1172-2-4
17. Zenker M, ed. Genotype-Phenotype Correlations in Noonan Syndrome. In: Monographs in Human Genetics. Vol 17. KARGER; 2008:40-54. https://doi.org/10.1159/000164838
18. Tangshewinsirikul C, Wattanasirichaigoon D, Tim-Aroon T, et al. Prenatal Sonographic Features of Noonan Syndrome: Case Series and Literature Review. JCM. 2024;13(19):5735. https://doi.org/10.3390/jcm13195735
19. Fowlkes JL, Thrailkill KM, Bunn RC. RASopathies: The musculoskeletal consequences and their etiology and pathogenesis. Bone. 2021;152:116060. https://doi.org/10.1016/j.bone.2021.116060
20. Ilic N, *KRAS*ic S, Maric N, et al. Noonan Syndrome: Relation of Genotype to Cardiovascular Phenotype-A Multi-Center Retrospective Study. Genes (Basel). 2024;15(11):1463. https://doi.org/10.3390/genes15111463
21. Pandit B, Sarkozy A, Pennacchio LA, et al. Gain-of-function *RAF1* mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. Nat Genet. 2007;39(8):1007-12. https://doi.org/10.1038/ng2073
22. Kobayashi T, Aoki Y, Niihori T, et al. Molecular and clinical analysis of *RAF1* in Noonan syndrome and related disorders: dephosphorylation of serine 259 as the essential mechanism for mutant activation. Hum Mutat. 2010;31(3):284-94. https://doi.org/10.1002/humu.21187
23. Saint-Laurent C, Mazeyrie L, Yart A, Edouard T. Novel therapeutic perspectives in Noonan syndrome and RASopathies. Eur J Pediatr. 2024;183(3):1011-9. https://doi.org/10.1007/s00431-023-05263-y
24. De Brouchoven I, Lorand J, Bofferding L, Sorlin A, Van Damme A, Danhaive O. Trametinib as a targeted treatment in cardiac and lymphatic presentations of Noonan syndrome. Front Pediatr. 2025;13:1475143. https://doi.org/10.3389/fped.2025.1475143
25. Sleutjes J, Kleimeier L, Leenders E, Klein W, Draaisma J. Lymphatic Abnormalities in Noonan Syndrome Spectrum Disorders: A Systematic Review. Mol Syndromol. 2022;13(1):1-11. https://doi.org/10.1159/000517605
26. Naylor PE, Bruno JL, Shrestha SB, et al. Neuropsychiatric phenotypes in children with Noonan syndrome. Dev Med Child Neurol. 2023;65(11):1520-9. https://doi.org/10.1111/dmcn.15627
27. Pascual-Morena C, Martínez-García I, Lucerón-Lucas-Torres M, et al. Prevalence of neurodevelopmental and psychiatric disorders in Noonan syndrome: a systematic review and meta-analysis. Eur J Pediatr. 2025;184(12):800. https://doi.org/10.1007/s00431-025-06648-x
28. Perrino MR, Das A, Scollon SR, et al. Update on Pediatric Cancer Surveillance Recommendations for Patients with Neurofibromatosis Type 1, Noonan Syndrome, *CBL* Syndrome, Costello Syndrome, and Related RASopathies. Clinical Cancer Research. 2024;30(21):4834-43. https://doi.org/10.1158/1078-0432.CCR-24-1611
29. Sodero G, Cipolla C, Pane LC, et al. Efficacy and safety of growth hormone therapy in children with Noonan syndrome. Growth Hormone & IGF Research. 2023;69-70:101532. https://doi.org/10.1016/j.ghir.2023.101532
30. Pierpont MEM, Magoulas PL, Adi S, et al. Cardio-Facio-Cutaneous Syndrome: Clinical Features, Diagnosis, and Management Guidelines. Pediatrics. 2014;134(4):e1149-e1162. https://doi.org/10.1542/peds.2013-3189
31. Roberts A, Allanson J, Jadico SK, et al. The cardiofaciocutaneous syndrome. J Med Genet. 2006;43(11):833-42. https://doi.org/10.1136/jmg.2006.042796
32. Abe Y, Aoki Y, Kuriyama S, et al. Prevalence and clinical features of Costello syndrome and cardio-facio-cutaneous syndrome

in Japan: Findings from a nationwide epidemiological survey. American J of Med Genetics Pt A. 2012;158A(5):1083-94. https://doi.org/10.1002/ajmg.a.35292

33. Feng B, Li X, Zhang Q, et al. Molecular and phenotypic spectrum of cardio-facio-cutaneous syndrome in Chinese patients. Orphanet J Rare Dis. 2023;18(1):284. https://doi.org/10.1186/s13023-023-02878-0
34. Scorrano G, David E, Calì E, et al. The Cardiofaciocutaneous Syndrome: From Genetics to Prognostic-Therapeutic Implications. Genes. 2023;14(12):2111. https://doi.org/10.3390/genes14122111
35. Bessis D, Morice-Picard F, Bourrat E, et al. Dermatological manifestations in cardiofaciocutaneous syndrome: a prospective multicentric study of 45 mutation-positive patients. Br J Dermatol. 2019;180(1):172-80. https://doi.org/10.1111/bjd.17077
36. Pierpont EI, Kenney-Jung DL, Shanley R, et al. Neurologic and neurodevelopmental complications in cardiofaciocutaneous syndrome are associated with genotype: A multinational cohort study. Genetics in Medicine. 2022;24(7):1556-66. https://doi.org/10.1016/j.gim.2022.04.004
37. Battaglia DI, Gambardella ML, Veltri S, et al. Epilepsy and *BRAF* Mutations: Phenotypes, Natural History and Genotype-Phenotype Correlations. Genes (Basel). 2021;12(9):1316. https://doi.org/10.3390/genes12091316
38. Di Majo BE, Leoni C, Cartisano E, et al. Cardiofaciocutaneous syndrome and immunodeficiency: data from an international multicenter cohort. Front Immunol. 2025;16:1598896.https://doi.org/10.3389/fimmu.2025.1598896
39. Gripp KW, Morse LA, Axelrad M, et al. Costello syndrome: Clinical phenotype, genotype, and management guidelines. American J of Med Genetics Pt A. 2019;179(9):1725-44. https://doi.org/10.1002/ajmg.a.61270
40. Rauen K. *HRAS* and the Costello syndrome. Clinical Genetics. 2007;71(2):101-8. https://doi.org/10.1111/j.1399-0004.2007.00743.x
41. Bessis D, Bursztejn A, Morice-Picard F, et al. Dermatological manifestations in Costello syndrome: A prospective multicentric study of 31 *HRAS* -positive variant patients. Acad Dermatol Venereol. 2024;38(9):1818-27. https://doi.org/10.1111/jdv.19996
42. Machida M, Rocos B, Taira K, et al. Costello syndrome-associated orthopaedic manifestations focussed on kyphoscoliosis: a case series describing the natural course. J Pediatr Orthop B. 2023;32(4):357-62. https://doi.org/10.1097/BPB.0000000000001013
43. Shankar SP, Fallurin R, Watson T, et al. Ophthalmic manifestations in Costello syndrome caused by Ras pathway dysregulation during development. Ophthalmic Genetics. 2022;43(1):48-57. https://doi.org/10.1080/13816810.2021.1978103
44. Peschiaroli S, Viscogliosi G, Salerni A, et al. Costello Syndrome and Ophthalmologic Issues: Unveiling the Unseen. American J of Med Genetics Pt A. 2025;197(7):e64049. https://doi.org/10.1002/ajmg.a.64049
45. Astiazaran-Symonds E, Ney GM, Higgs C, et al. Cancer in Costello syndrome: a systematic review and meta-analysis. Br J Cancer. 2023;128(11):2089-96. https://doi.org/10.1038/s41416-023-02229-7
46. Narumi Y, Aoki Y, Niihori T, et al. Molecular and clinical characterization of cardio-facio-cutaneous (CFC) syndrome: Overlapping clinical manifestations with Costello syndrome. American J of Med Genetics Pt A. 2007;143A(8):799-807. https://doi.org/10.1002/ajmg.a.31658
47. Gelb BD, Tartaglia M. Noonan Syndrome with Multiple Lentigines. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews®. University of Washington, Seattle; 1993. Accessed March 4, 2026. http://www.ncbi.nlm.nih.gov/books/NBK1383/
48. Monda E, Prosnitz A, Aiello R, et al. Natural History of Hypertrophic Cardiomyopathy in Noonan Syndrome With Multiple Lentigines. Circ: Genomic and Precision Medicine. 2023;16(4):350-8. https://doi.org/10.1161/CIRCGEN.122.003861
49. Gao X, Huang SS, Qiu SW, et al. Congenital sensorineural hearing loss as the initial presentation of *PTPN11*-associated Noonan syndrome with multiple lentigines or Noonan syndrome: clinical features and underlying mechanisms. J Med Genet. 2021;58(7):465-74. https://doi.org/10.1136/jmedgenet-2020-106892
50. Liu Z, Lai J, Song F. Noonan syndrome and Noonan-like syndrome with loose anagen hair: rare phenotypes may emerge during follow-up. Transl Pediatr. 2024;13(7):1161-8. https://doi.org/10.21037/tp-24-113
51. Wang XO, Liu ZQ, Shangguan SF, et al. [Clinical characteristics analysis of children with Noonan-like syndrome with loose anagen hair]. Zhonghua Er Ke Za Zhi. 2025;63(4):405-10. https://doi.org/10.3760/cma.j.cn112140-20241010-00706
52. Gripp KW, Aldinger KA, Bennett JT, et al. A novel rasopathy caused by recurrent de novo missense mutations in *PPP1CB* closely resembles Noonan syndrome with loose anagen hair. Am J Med Genet A. 2016;170(9):2237-47. https://doi.org/10.1002/ajmg.a.37781
53. Leoni C, Viscogliosi G, Tartaglia M, Aoki Y, Zampino G. Multidisciplinary Management of Costello Syndrome: Current Perspectives. J Multidiscip Healthc. 2022;15:1277-96. https://doi.org/10.2147/JMDH.S291757
54. Wolf CM, Zenker M, Boleti O, et al. Impact of MEK Inhibition on Childhood RASopathy-Associated Hypertrophic Cardiomyopathy. JACC: Basic to Translational Science. 2025;10(2):152-66. https://doi.org/10.1016/j.jacbts.2024.10.002
55. Dionysiou M, Makri SC, Ahlawat S, et al. Case report: MEK inhibitor as treatment for multi-lineage mosaic *KRAS* G12D-associated epidermal nevus syndrome in a pediatric patient. Front Neurol. 2024;15:1466946. https://doi.org/10.3389/fneur.2024.1466946
56. D'Onofrio G, Delrue MA, Lortie A, et al. Treatment of Refractory Epilepsy With MEK Inhibitor in Patients With RASopathy. Pediatric Neurology. 2023;148:148-51. https://doi.org/10.1016/j.pediatrneurol.2023.08.019
57. Krishna MR, Sennaiyan UN. Everolimus therapy in an infant with Noonan syndrome with multiple lentigines. Ann Pediatr Cardiol. 2025;18(1):72-4. https://doi.org/10.4103/apc.apc_26_25
58. Cormier F, Lara-Corrales I, Sauder M, Levy R. Therapeutic Advances in Neurofibromatosis Type 1: A Focus on Selumetinib. Skin Therapy Lett. 2025;30(5):1-4.
59. De Blank PMK, Gross AM, Akshintala S, et al. MEK inhibitors for neurofibromatosis type 1 manifestations: Clinical evidence and consensus. Neuro-Oncology. 2022;24(11):1845-56. https://doi.org/10.1093/neuonc/noac165
60. Khalid A, Denton K, Paria N, et al. MEK inhibitor Mirdametinib promotes fracture healing in osteofibrous dysplasia RASopathy. J Clin Invest. 2026;136(9):e199048. https://doi.org/10.1172/JCI199048.