Clinical manifestations of mutations in RAS and related intracellular signal transduction factors

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Purpose of review

Recent advances in molecular genetic research have led to the definition of the new group of genetic syndromes, the RAS–mitogen-activated protein kinase (MAPK) pathway disorders or 'RASopathies'. They comprise Noonan syndrome and related disorders (cardio-facio-cutaneous and Costello syndromes), as well as neurofibromatosis type 1. This review summarizes the recent literature with a special focus on genotype–phenotype correlations.

Recent findings

Although the picture is still incomplete, and additional genes are likely to exist, the underlying genetic alteration can now be found in a large majority of patients with a RASopathy phenotype. The most recently discovered novel genes for Noonan syndrome or Noonan syndrome-like disorders, *NRAS*, *SHOC2*, and *CBL*, account for small fractions of the patient population. The increasing knowledge about the spectrum of gene mutations and associated clinical manifestations has led to a refinement of genotype–phenotype correlations. Recent studies have added new insights into tumor predisposition and prenatal manifestations. Model systems are being developed to investigate innovative treatment approaches.

Summary

Constitutional overactivation at various levels of the RAS–MAPK pathway causes overlapping syndromes, comprising characteristic facial features, cardiac defects, cutaneous abnormalities, growth deficit, neurocognitive delay, and predisposition to malignancies. Each syndrome also exhibits unique features that probably reflect genotype-related specific biological effects.

Keywords

cardio-facio-cutaneous syndrome, Costello syndrome, neurofibromatosis type 1, Noonan syndrome, RAS–mitogen-activated protein kinase pathway

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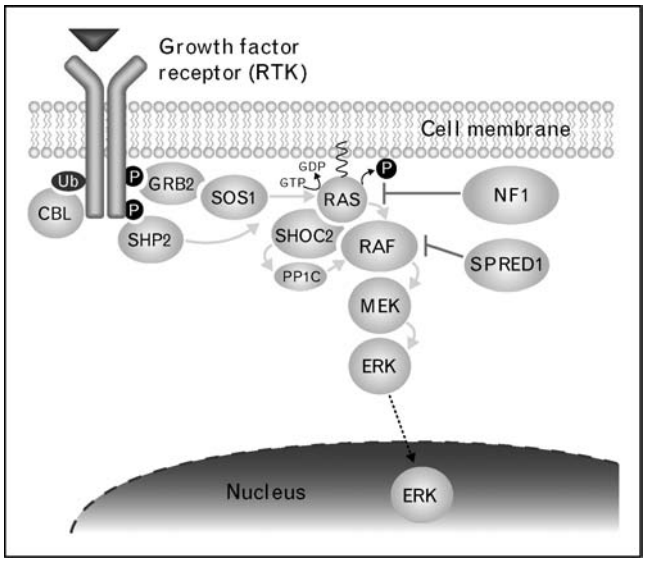
Introduction

During recent years, a new class of genetic diseases has emerged that includes Noonan syndrome, one of the most common monogenic disorders in humans, and the clinically overlapping disorders such as cardio-facio-cutaneous (CFC) and Costello syndromes. Although genetic studies have revealed an unforeseen molecular and clinical heterogeneity of these disorders, the common denominator is that all the involved genes encode components or modulators of the RAS–mitogen-activated protein kinase (MAPK) pathway [1••,2,3]. This pathway also links Noonan syndrome and related disorders to neurofibromatosis type 1 (NF1). The entire group is subsumed under the term RAS–MAPK pathway disorders, neuro-facial-cardial-cutaneous disorders, or RASopathies.

The RAS–mitogen-activated protein kinase signaling pathway and its involvement in tumorigenesis and developmental disorders

RAS-GTPases are ubiquitous molecules that act as central molecular switches by cycling between an active GTP-bound and an inactive GDP-bound form [4]. Through association with RAF, GTP-bound RAS initiates an activation cascade of MAPKs (Fig. 1). The balance of RAS activation and inactivation is finely regulated. The RAS–MAPK pathway is characterized by molecular redundancy including several RAS, RAF, MEK, and ERK (extracellular signal-regulated kinase) isoforms encoded by different genes. *RAS* and *RAF* genes have long been known as proto-oncogenes [5]. Somatic mutations in *KRAS* and *BRAF* belong to the most common genetic alterations observed in a variety of malignancies.

Figure 1 Signal transduction through the RAS–mitogen-activated protein kinase pathway



Upon recruitment to activated growth factor receptors, guanine nucleotide exchange factors such as SOS1 activate RAS through facilitating the exchange of GDP by GTP. GTP-bound RAS can initiate an activation cascade of mitogen-activated protein kinases, RAF, MEK, and extracellular signal-regulated kinase (ERK). Restitution of RAS's inactive state is achieved by hydrolysis of GTP to GDP through the intrinsic GTPase activity of RAS, which is augmented by GTPase-activating proteins such as neurofibromin (NF1). Thereby, NF1 acts as negative regulator of RAS signaling. SHOC2 and SPRED1 are positive and negative modulators, respectively, at the level of the RAS–RAF interaction. CBL protein acts as an ubiquitin (Ub) ligase that can recognize tyrosine-phosphorylated substrates and, thereby, modulates receptor tyrosine kinase-mediated signal transduction.

Both mutations that occur as somatic lesions in tumors, as well as the germline changes associated with developmental disorders, are considered to cause dysregulated (i.e., overactive) RAS–MAPK signaling [1••,2]. Nevertheless, with few exceptions, their mutation spectra do not overlap. It has been experimentally proven for several mutant proteins [6•,7,8] and is believed as a general principle that mutations occurring in the germline cause less dysregulation of the pathway, one that is capable of perturbing developmental programs but unlikely to promote tumorigenesis. In contrast, the typical somatic oncogenic mutations result in stronger RAS–MAPK pathway overactivation that is thought to be lethal when occurring in the germline.

Common phenotypic features of the RASopathies

The phenotype of Noonan syndrome is prototypic for a pattern of physical and developmental anomalies that results from constitutional dysregulation of RAS–MAPK signaling. This pattern can be recognized in all RASopathies, although individual symptoms may vary considerably in their expression between the different entities. Congenital heart defects, short stature, and distinctive craniofacial features are hallmarks of the Noonan syndrome/RASopathy phenotype [3]. The most typical heart defects include valvular pulmonary stenosis often associated with valve dysplasia, hypertrophic cardiomyopathy (HCM), and atrioventricular septal defects [9].

Key points

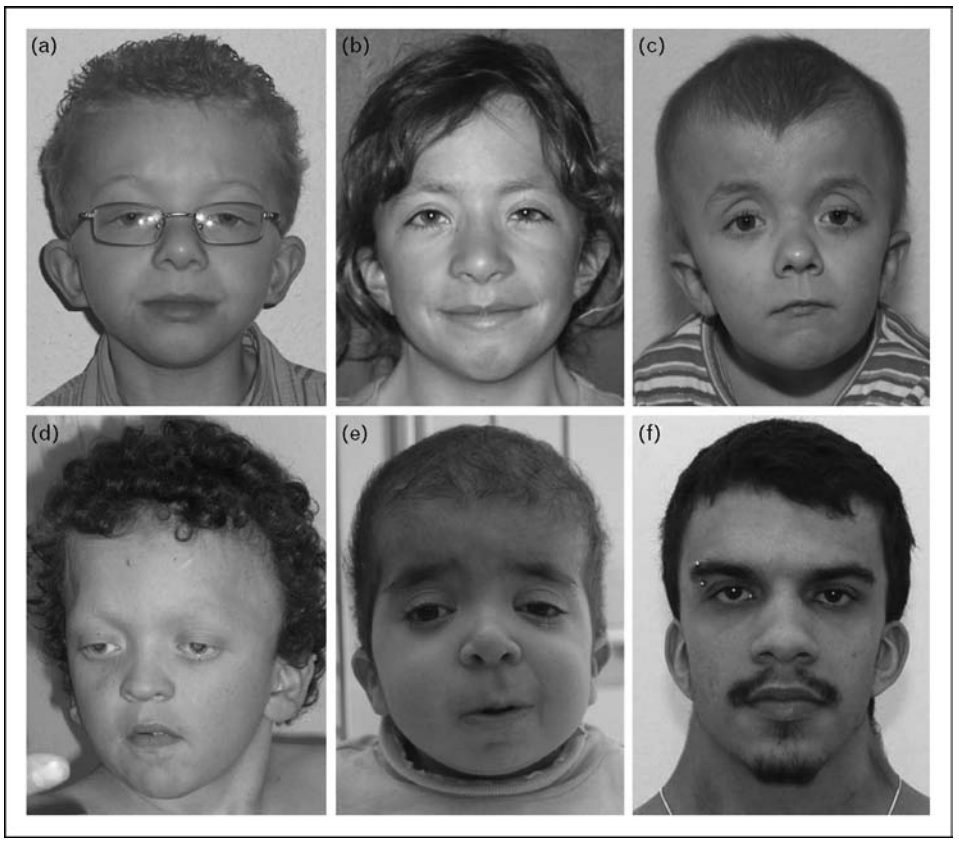
- Typical craniofacial anomalies together with certain congenital heart defects, short stature, variable cognitive deficits, and lymphatic and skeletal anomalies characterize a recognizable phenotype that is shared by the RAS–mitogen-activated protein kinase pathway disorders.
- The improving definition of genotype–phenotype correlations between and within the major disease categories, Noonan, cardio-facio-cutaneous, and Costello syndrome, is making genetic testing an increasingly useful tool for differential diagnosis, as well as individual prognostic estimation.
- The preliminary evidence of a variably increased cancer risk in apparently all RASopathies demands further studies to substantiate and specify risk figures and tumor spectrum.
- Current and future research on tissue and animal model systems may shed light on potential therapies targeting RAS pathway overactivation or dependent signaling events.

The abnormal growth pattern is characterized by normal or slightly subnormal measurements at birth, postnatal decline in height standard deviation score and often attenuated and delayed pubertal growth spurt, which may lead to some catch-up growth in early adulthood [10]. Adult height varies among different entities. Head size is usually increased (relative or absolute macrocephaly).

The typical craniofacial anomalies are illustrated in Fig. 2 [11]. The craniofacial features may be difficult to appreciate in newborns and become subtler during adolescence [12].

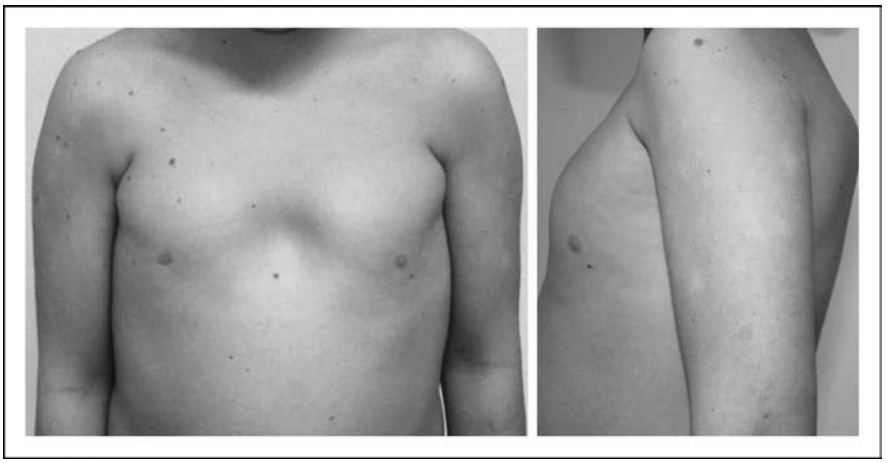
Various additional anomalies occur frequently in RAS–MAPK pathway disorders. They include lymphatic anomalies that may result in a wide spectrum of postnatal (lymphedema, chylothorax) or prenatal (see below) manifestations. A characteristic thorax shape is common (Fig. 3) [11], as well as cryptorchidism in males. Ectodermal features are variable and include dry skin with hyperkeratotic changes (follicular hyperkeratosis, rarely palmar/plantar hyperkeratosis), curly and/or sparse, slow-growing hair, and pigmentary changes (*café-au-lait* macules, lentigines). Less specific but common features are ocular anomalies

Figure 2 Similarities of craniofacial features of Noonan syndrome and other RASopathies



Similarities of (a–c) Noonan syndrome and (d–f) other RASopathies include hypertelorism with downward slanting palpebral fissures, ptosis of the eyelids, a broad forehead, low-set and posteriorly rotated ears, and a broad neck/pterygium colli. Curly or sparse hair and sparse eyebrows can be appreciated in some of the depicted patients. The individual diagnoses of the depicted patients are as follows: (a) Noonan syndrome due to a mutation of *PTPN11*, (b) *SOS1*, and (c) *SHOC2*, respectively; (d) cardio-facio-cutaneous syndrome with a *BRAF* mutation; (e) Costello syndrome due to a *HRAS* mutation; and (f) neurofibromatosis-Noonan syndrome. Reproduced in part with permission from [11].

Figure 3 Typical thorax deformity in a patient with Noonan syndrome



Deformities seen are wide-spaced nipples, pectus carinatum superiorly, and excavatum inferiorly. Reproduced with permission from [11].

Table 1 Typical clinical features of the RASopathies

Heart	Pulmonary valve stenosis/dysplasia, hypertrophic cardiomyopathy, atrial septal defect, ventricular septal defect, and various other heart defects occasionally observed
Feeding and growth	Feeding difficulties, postnatal growth retardation, proportionate short stature, and relative or absolute macrocephaly
Craniofacial	Hypertelorism, down-slanting palpebral fissures, ptosis, broad forehead, low-set and/or posteriorly rotated ears, and short and broad neck/pterygium colli
Genitourinary	Cryptorchidism and minor renal anomalies
Skeletal	Thorax deformity: broad thorax, pectus carinatum superiorly and excavatum inferiorly, and scoliosis
Skin and adnexa	Dry, hyperkeratotic skin, keratosis pilaris, palmoplantar keratosis, ulerythema ophryogenes, pigmented skin lesions, curly, sparse, and/or slow-growing hair
Development	Motor delay, muscular hypotonia, mental retardation, learning difficulties
Ocular	Refractive errors, strabismus, and nystagmus
Lymphatic	Fetal nuchal edema, fetal hydrothorax, hydrops, and neonatal or postnatal lymphedema
Coagulation	Easy bruising and variable partial deficiencies of coagulation factors (factors VIII, XI, XII, and von Willebrand factor)
Oncologic	Juvenile myelomonocytic leukemia, multiple giant cell lesions, and various other malignancies occasionally observed

(strabismus, nystagmus, refractive errors) and mild bleeding diathesis. Many patients are poor feeders during infancy. Muscular hypotonia and delay in motor milestones are common findings. Cognitive impairment is frequent, but varies strongly among the different RASopathies [3]. The clinical phenotype of Noonan syndrome has been the subject of several excellent reviews [13,14,15••,16]. A brief synopsis is given in Table 1.

The various genetic etiologies of RASopathies and genotype–phenotype correlations

The search for genes responsible for Noonan syndrome and related disorders started 10 years ago and has revealed an unforeseen genetic heterogeneity [1••,2,3]. The most recent discoveries identified *SHOC2* [17], *NRAS* [6•], and *CBL* [18•] as genes for rare cases of Noonan syndrome or Noonan syndrome-like disorders. Notably, the molecular genetic findings have largely confirmed and, at some points, refined the established nosology. Distinct clinical syndromes are caused by mutations in specific genes or even by specific types of mutations with only small areas of overlap (Table 2). However, the following narrative is still a relatively crude snapshot and we will probably learn about additional genes and individual mutations associated with specific phenotypic features in the future.

Noonan syndrome (*OMIM* 163950)

Overall, 50–80% of Noonan syndrome patients have heart defects, 50–70% have short stature, and about

Table 2 Genotype–phenotype correlations

Entity	Mutated gene(s)[a]	Distinctive features
Noonan syndrome	***PTPN11***, ***SOS1***, ***RAF1***, *KRAS*, *NRAS*, *MEK1*, *BRAF*, *CBL*	Minor cognitive deficits Easy bruising
Noonan syndrome-like disorder with loose anagen hair	***SHOC2***	Hair phenotype Dark skin pigmentation Semilunar valve dysplasias Growth hormone deficiency
Noonan syndrome-like disorder with JMML	***CBL***	Increased risk of JMML Variable Noonan syndrome-like features
NSML/LEOPARD syndrome	***PTPN11*** (specific mutations), *RAF1*, *BRAF*	Multiple lentigines Hypertrophic cardiomyopathy Sensorineural deafness
CFC syndrome	***BRAF***, ***MEK1***, ***MEK2***, *KRAS*, *SOS1*	Mental retardation (mild to severe) Hyperkeratotic skin changes Curly/wooly hair
Costello syndrome	***HRAS***	Mental retardation (mild to moderate) Sparse/curly hair Deep palmar/plantar creases Soft, redundant skin Ulnar deviation at the wrists Severe feeding difficulties Atrial tachycardia
Neurofibromatosis NF1-Noonan syndrome	***NF1***	*Café-au-lait* spots, freckling Neurofibroma Variable Noonan syndrome-like features
Legius syndrome	***SPRED1***	*Café-au-lait* spots, freckling No tumors typical of NF1 Variable Noonan syndrome-like features

CFC, cardio-facio-cutaneous; JMML, juvenile myelomonocytic leukemia; NF1, neurofibromatosis type 1; NSML, Noonan syndrome with multiple lentigines.
[a] More frequently mutated genes printed in bold and rarely mutated genes (<5%) in normal letters.

one-third show cognitive deficits requiring special education [13,14,15••,16]. The average intelligence quotient level in patients with Noonan syndrome is around 80–90 [19,20].

PTPN11 was the first identified gene for Noonan syndrome [21] and is the most frequently mutated one, accounting for 40–50% of cases. *PTPN11* (*OMIM* 176876) encodes SHP2 and acts upstream of RAS (as does SOS1), as depicted in Fig. 1. Patients carrying *PTPN11* mutations are more likely to have pulmonary stenosis and less likely to have HCM [22,23]. Easy bruising is more often observed in patients with *PTPN11* mutations compared with other genotypes.

SOS1 mutations are responsible for 10–15% of cases with Noonan syndrome [24,25]. These patients display a similar spectrum of heart defects to patients with *PTPN11* mutations, but they are less likely to have short stature and to require special education. Ectodermal abnormalities (curly hair, sparse eyebrows, keratosis pilaris) are more common in patients with mutated *SOS1* and may be reminiscent of CFC syndrome [26•].

RAF1 mutations account for 5–8% of cases with Noonan syndrome and are strongly associated with HCM [27,28]. Eighty to 95% of patients with *RAF1* mutations have HCM that may in some instances be associated with a fatal course in infancy.

KRAS mutations are rare in Noonan syndrome (about 2–3%) [7]. The associated phenotype is quite variable and patients have been classified as having either Noonan or CFC or even Costello syndrome [29]. Cognitive impairment is more common in patients with *KRAS* mutations than generally seen in Noonan syndrome. No clear correlations between specific *KRAS* mutations and phenotypic classifications have emerged so far. *NRAS* mutations account for fewer than 0.5% of cases with Noonan syndrome [6•]. The few reported cases do not suggest any specific phenotype.

BRAF and *MEK1* mutations, which usually cause CFC syndrome (see below), have exceptionally been reported in Noonan syndrome [30,31]. There is some evidence that certain *BRAF* and *MEK1* mutations are associated with a milder phenotype (particularly with milder cognitive impairments), which is more likely to be classified as Noonan syndrome [30–32]. Further genotype–phenotype studies are required to support this notion.

Noonan syndrome with multiple lentigines/LEOPARD syndrome (*OMIM* 151100)

Noonan syndrome with multiple lentigines (NSML) is the term that is now preferred over LEOPARD syndrome, which was coined as an acronym for multiple lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, retardation of growth, and deafness [33]. Although young children with NSML are initially often diagnosed with Noonan syndrome, the development of multiple lentigines, which usually starts in childhood, allows distinguishing NSML from Noonan syndrome. Moreover, patients with NSML more often have HCM (up to 80%) than pulmonary stenosis (10–40%), and sensorineural deafness occurs in 15–25%. The frequency and the level of cognitive and growth deficits appear to be similar to Noonan syndrome [34].

NSML is also genetically distinct from Noonan syndrome. Specific *PTPN11* mutations (mainly p.Y279C, p.T486M) are responsible for the majority of NSML cases. In contrast to Noonan syndrome-associated *PTPN11* mutations, these changes result in reduced catalytic activity of the gene product SHP2. Nonetheless, NSML-associated *PTPN11* alterations are obviously not simple loss-of-function mutations leading to haploinsufficiency. Dominant-negative effects have been proposed [35] as well as gain-of-function effects that are independent of SHP2 catalytic function [36–38]. Mutations in *RAF1* [27] and *BRAF* [32] have rarely been reported with a NSML phenotype.

Noonan syndrome-like with loose anagen hair (*OMIM* 607721)

A Noonan syndrome-like disorder with a characteristic hair phenotype was recently proposed as a separate entity by Mazzanti *et al.* [39]. The hair in these patients is easily pluckable, sparse, thin, and slowly growing. Trichogram from pull test usually shows the majority to be anagen hairs. This syndrome is furthermore characterized by diffuse skin hyperpigmentation, a typical spectrum of heart defects (semilunar valve dysplasias and septal defects overrepresented compared with pulmonary stenosis and HCM), more severe growth deficits frequently associated with growth hormone deficiency, a higher frequency of cognitive and behavioral issues, and recognizable craniofacial features (Fig. 1c).

The Noonan syndrome-like disorder with loose anagen hair has been found to be genetically homogeneous and distinct. A single and functionally unique mutation in the gene *SHOC2*, p.S2G, accounts for virtually all cases with this specific phenotype [17].

Noonan syndrome-like disorder with juvenile myelomonocytic leukemia (*OMIM* 613563)

Heterozygous germline mutations in the *CBL* gene have simultaneously been discovered in patients with juvenile myelomonocytic leukemia (JMML) and additional features suggestive of an underlying developmental disorder that was more or less reminiscent of Noonan syndrome

[40••,41], as well as in a cohort with a Noonan syndrome or a Noonan syndrome-like phenotype without hematologic abnormalities [18•]. The phenotype associated with *CBL* mutations is relatively variable and includes impaired growth, developmental delay, cryptorchidism in males, and predisposition to JMML. *CBL* mutations show incomplete penetrance, as evidenced by several instances of inheritance of the disease-causing mutation from an apparently healthy parent [18•,40••,41].

Neurofibromatosis-Noonan syndrome (*OMIM* 601321)

The term neurofibromatosis-Noonan syndrome (NFNS) was introduced for patients fulfilling clinical criteria for NF1 [42] and additionally exhibiting typical manifestations of Noonan syndrome (such as craniofacial anomalies, short stature, and learning difficulties) [43]. The presence of the typical NF1-associated skin lesions and tumors clearly distinguishes NFNS from Noonan syndrome. Patients with NFNS usually carry mutations in the *NF1* gene. It has been postulated that specific types of *NF1* mutations might be overrepresented in NFNS, suggesting genotype–phenotype correlations [44]. Others speculated the NFNS phenotype might just represent the extreme of a highly variable spectrum of the expression of Noonan syndrome-like features in patients with NF1 [45]. In fact, NF1 in general is quite commonly associated with developmental anomalies that fit into the spectrum of Noonan syndrome. These include learning difficulties that affect more than half of NF1 patients [46,47], short stature (present in 20% [48]), and even heart defects of the Noonan syndrome spectrum that occur more frequently in NF1 than in the normal population [49]. Facial anomalies reminiscent of Noonan syndrome can be recognized in a considerable proportion of NF1 patients [45,50]. It is assumed that all the developmental anomalies seen in patients with NF1 that overlap those of the Noonan syndrome phenotype reflect a slight but generalized dysregulation of the RAS-MAPK pathway due to haploinsufficiency caused by the germline mutation of one *NF1* allele [45]. In contrast, pigmented skin lesions and the typical tumors, which represent the main clinical criteria of NF1 [42], have been shown to result from a somatic loss of function of the second allele and clonal expansion of cells that are completely devoid of neurofibromin-induced inhibition of the RAS-MAPK pathway [51].

Legius syndrome (*OMIM* 611431)

A NF1-like disorder that is characterized by multiple *café-au-lait* spots but absence of NF1-associated tumors was genetically elucidated in 2007 [52]. Affected individuals may show some Noonan syndrome-like features such as subtle craniofacial anomalies, learning difficulties, and growth deficit. The gene *SPRED1* that causes Legius syndrome encodes a negative regulator of the RAS–MAPK pathway. Similarly to NF1, the *SPRED1* germline mutations cause loss of function, suggesting that the Noonan syndrome-like features reflect haploinsufficiency.

Cardio-facio-cutaneous syndrome (*OMIM* 115150)

CFC syndrome can be distinguished from Noonan syndrome mainly by a more severe cognitive impairment and more prominent ectodermal anomalies [24,53••]. The cognitive abilities of the majority of patients fall in the range of mild-to-severe mental retardation. Epilepsy occurs in about half of the cases and various structural brain abnormalities have been described [54]. Skin and adnexal changes are present in virtually all patients with CFC syndrome [55]. They include follicular hyperkeratosis, sparse, slow-growing, curly hair, palmoplantar hyperkeratosis at the pressure zones, and development of multiple pigmented nevi. The spectrum of heart defects is similar to that in Noonan syndrome.

CFC syndrome is caused by mutations in the genes *BRAF* (50–60%), *MEK1* (5–10%), *MEK2* (5–10%), and *KRAS* (3–5%) [56,57]. Preliminary genotype–phenotype correlations among these genes that have been proposed need to be further substantiated [53••].

Costello syndrome (*OMIM* 218040)

Patients with Costello syndrome constitute a relatively homogeneous group, genetically and clinically. It is now widely accepted that the term Costello syndrome should be reserved for patients with a *HRAS* mutation because of the specific risk profile of these patients [58]. More than 70% of patients with Costello syndrome harbor the same *HRAS* mutation (p.G12S) [58,59].

Patients with Costello syndrome usually show severe feeding problems in infancy. During childhood, the patients develop coarser facial features than usually seen in Noonan syndrome, which may suggest a storage disorder. Skin is soft and redundant with deep palmar and plantar creases. Hair is sparse in early childhood and curly thereafter. Epidermal warts or papillomata may occur. Cognitive function is typically at the level of mild to moderate mental retardation [60]. The most frequent cardiac abnormalities are atrial tachycardia, HCM, and pulmonary stenosis [61•]. Notably, patients with Costello syndrome are at increased tumor risk (15–25%) with embryonal rhabdomyosarcoma, bladder carcinoma, and neuroblastoma representing the most commonly reported tumor entities [62].

New insights into tumor risk in Noonan syndrome

The demonstration that germline mutations in components of a central oncogenic pathway are responsible for Noonan syndrome has raised concerns about a

possible increased tumor risk. In contrast to NF1 and Costello syndrome, Noonan syndrome and the other related disorders have not been generally regarded as cancer predisposition disorders. In recent years, it has become evident that certain rare tumors or tumor-like lesions are specifically associated with RASopathies [63,64]. JMML, a rare myeloproliferative disease of childhood, is associated with Noonan syndrome as well as NF1, although the absolute prevalence in individuals affected by either of these disorders is quite low (about 1–2%) [65••]. Specific mutations (e.g., *PTPN11* p.T73I, and mutations in the *CBL* gene) have been identified as tumor risk genotypes for Noonan syndrome with JMML [40••,64]. Giant cell lesions affecting the jawbones or joints (pigmented villonodular synovitis) are tumor-like lesions that are also clearly associated with Noonan syndrome and other RASopathies [66]. Moreover, there is a large number of anecdotal reports on various types of neoplasias in patients with Noonan syndrome. A very recent comprehensive literature review identified neuroblastoma, acute lymphoblastic leukemia, low-grade glioma, and rhabdomyosarcoma as the most commonly reported tumors in Noonan syndrome [65••]. A recently published epidemiologic study from the Netherlands calculated a 3.5-fold increased risk of cancer in patients with Noonan syndrome and a *PTPN11* mutation compared with that in the general population [67•]. Despite various limitations of these studies, the current data suggest that Noonan syndrome may be associated with a broader spectrum of malignancies than previously appreciated and a mildly increased overall cancer risk. Larger epidemiologic studies are required to define more precisely tumor spectrum and risk figures. Current knowledge does not warrant specific cancer surveillance for patients with Noonan and CFC syndrome, but awareness and a low threshold for additional investigations in case of any unusual symptoms are appropriate.

Prenatal manifestations

Although many of the characteristic abnormalities defining Noonan syndrome are undetectable in the fetus, abnormal findings during pregnancy are quite common. The typical prenatal history includes fetal abnormalities that range from fetal nuchal edema/cystic hygroma to pleural effusions (chylothorax) and generalized hydrops. The prevalence of such abnormalities in fetuses affected by Noonan syndrome is not known, but, considering the high frequency of a short and broad neck with excess nuchal skin in newborns with RASopathies, it is tempting to speculate that nuchal edema is a common feature of affected fetuses. Pergament *et al.* [68•] identified eight cases of Noonan syndrome among 120 euploid fetuses with increased nuchal translucency. Previously, Lee *et al.* [69] even found *PTPN11* mutations in 12 of 134 euploid fetuses with abnormal ultrasound findings of the above-mentioned spectrum. Notably, the mutations observed in three fetuses with hydrops fetalis from this cohort had previously been reported as somatic cancer mutations, thus providing preliminary insights into manifestations of lethal RAS pathway mutations.

Future prospects regarding diagnosis and management

Diagnosis of the aforementioned disorders is primarily based on the recognition of the clinical phenotype and can in most cases (60–80% depending on clinical criteria) be confirmed by molecular genetic testing. Strategies have been proposed to prioritize the genes to test based on phenotypic criteria [15••]. However, the emerging new methods in genetic testing will probably soon overcome these issues. With more differentiated knowledge on genotype–phenotype correlations and pathophysiology, molecular genetic testing may become more useful not only for confirmation of the clinical diagnosis but also for prognostic estimation and management.

Current treatment options for RASopathies are solely symptomatic. Multidisciplinary management and a lifelong follow-up for late manifestations and complications are basic elements of the published management recommendations [15••,53••,58]. Medical treatment approaches using compounds that compensate the consequences of disturbed RAS-mediated signaling have successfully been used in animal and in-vitro models to target cognitive impairment [70,71] and HCM [72•,73•]. Treatment studies on humans are awaited.

Conclusion

The diseases caused by mutations in RAS and related intracellular signal transduction factors include relatively common monogenic disorders and range from mild conditions that may only marginally affect life quality and expectancy to severely disabling syndromes. Their common pathophysiological denominator is constitutional dysregulation of the RAS–MAPK pathway, which may result from mutations in multiple genes. Translation of these genetic findings into clinical applications is creating a very exciting new area of research. The improved understanding of the genetic and molecular mechanisms underlying Noonan syndrome, CFC syndrome, Costello syndrome, and other related diseases will likely permit the development of improved diagnostic and therapeutic approaches for these patients in the future.

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