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RASopathies

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Abstract RASopathies are a group of disorders characterized by mutations in the RAS-MAPK pathway. RAS-MAP signaling plays a critical role in cell differentiation, proliferation, and survival. Germline mutations can result in distinctive syndromes, including Noonan syndrome, Costello syndrome, and neurofibromatosis type 1. Mosaic RASopathies can present as localized cutaneous lesions like epidermal nevi and nevus sebaceous, or more extensive conditions such as encephalocraniocutaneous lipomatosis. We review the heterogenous presentation of RAS mutations, discuss new targeted therapies, and highlight areas of uncertainty, including carcinogenesis risk and appropriate screening.

Introduction

Ras proteins are GTPases that play critical roles in cellular signaling.[1] The most clinically significant Ras pathways involve *Ras-Raf-MEK-ERK* and *PI3K-Akt*.[2] Three genes encode the best-studied Ras proteins: *HRAS*, *KRAS*, and *NRAS*. Activation of pathways can have myriad effects on cell survival/apoptosis, differentiation, and proliferation. Disturbance of Ras function at the germline level can result in well-characterized syndromes, often with overlapping features; somatic or mosaic mutations may lead to different but equally distinctive phenotypes[3] (Tables 1 and 2). Activating *RAS* mutations are found in up to 30% of human cancers.[4] Recognition of these related syndromes is essential for appropriate management. Both germline and mosaic presentations are discussed, along with their management, including newer targeted therapies.

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Germline RASopathies

Noonan syndrome

Noonan syndrome is a germline RASopathy, resulting from an autosomal dominant gain-of-function mutation in the *PTPN11* gene on chromosome 12. Mutated *PTPN11* leads to an overproduction of the RAS-MAP regulator SPH-2, which in turn causes abnormal tissue growth and replication.[1] The incidence of Noonan syndrome is estimated to range between 1-in-1000 and 1-in-2500.[5]

Noonan syndrome can be recognized by its unique facial features: large cranium, high forehead, narrowing of the temples, and a high peaked vermilion.[6] Chest deformities, primarily pectus carinatum and excavatum, are very common in patients with Noonan syndrome, as is short stature.[7] Patients with Noonan syndrome also often suffer from mental retardation, bleeding diatheses,[8] and cryptorchidism.

Cutaneous manifestations include a low hairline, slow beard growth, and sparse pubic and axillary hair.[9] Nails are short and broad. Melanocytic nevi are common.[9] Lower

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Table 1 Germline RASopathies.

Disease	Affected gene	Inheritance type	Cutaneous signs
Noonan syndrome	*PTPN11* (chromosome 12)	Autosomal dominant gain-of-function	Low hairline, slow beard growth and sparse pubic and axillary hair, short and broad nails, melanocytic nevi
Noonan-NF-1 syndrome	*PTPN11* or *NF-1*	Unknown	Café-au-lait spots, Lisch nodules, axillary freckling, neurofibromas,
Noonan syndrome with multiple lentigines (previously LEOPARD syndrome)	*PTPN11* (90%) or *RAF1* (10%)	Unknown	Generalized café-au-lait during first year, black-brown macule lentigines of upper body during teenage years
Costello syndrome	*HRAS*	Autosomal dominant gain-of-function	Cutis laxa, hyperpigmentation, hyperkeratosis, centrofacial papillomas
Cardiofaciocutaneous syndrome	*BRAF* or *MAP2K1/2*	[redacted] dominant	Dystrophic nails, hyperkeratosis, thin eyebrows, keratosis pilaris, severe xerosis
Neurofibromatosis type 1 (Von Recklinghausen disease)	*NF-1* microdeletion at 17q11.2	Autosomal dominant	Café-au-lait macules, solar lentigines, axillary freckling, neurofibromas
Legius syndrome	*SPRED1*	Autosomal dominant gain-of-function	Café-au-lait macules, intertriginous freckling

extremity lymphedema and stasis dermatitis are common in adults, whereas infants may present with transient lymphedema of their extremities, which can permit an early diagnosis.[7] This transient subcutaneous lymphedema commonly presents on the dorsal surfaces of hands and feet, can have associated dermatoglyphic alteration such as increased whorls on fingertips, and is thought to be secondary to congenital lymphatic dysplasia.[10] Xerosis and keratosis pilaris are also common.

Noonan syndrome-neurofibromatosis type 1

Noonan syndrome–neurofibromatosis type 1 (NS-NF-1) presents with phenotypic overlap between Noonan syndrome and neurofibromatosis type 1.[11] Affected individuals often have signature ectodermal features of NF-1, including café-au-lait spots, Lisch nodules, axillary freckling, and neurofibromas, with the NS clinical manifestations of growth retardation, hypertelorism, congenital heart defects, and pectus excavatum/carinatum.[11,12] Genetically, there is still uncertainty whether this condition is caused by a mutation in *NF-1,* the mutated gene in patients with neurofibromatosis type I, or in *PTPN11,* the mutated gene in patients with Noonan syndrome.[13]

A recent study found that 16 of the 17 patients had a mutation in the *NF-1* gene, including nonsense mutations, frameshift deletions, and missense changes[14]; none had *PTPN11* mutations, suggesting that the NS-NF-1 overlap is likely a *forme fruste* of NF-1.

Noonan syndrome with multiple lentigines

Noonan syndrome with multiple lentigines (previously known as LEOPARD syndrome) is the second most common neuro-cardio-facial-cutaneous syndrome after Noonan syndrome,[5] with roughly 200 cases reported worldwide, though many more are suspected to have gone unreported.[15] The disease has a similar *PPTN11* gene mutation on chromosome 12 in 90% of patients, but 10% of patients have been found to have a mutation in the *RAF1* gene.[16] The variants of *PTPN11* mutation seen in Noonan syndrome with multiple lentigines show increased and prolonged activity not only in the RAF signaling pathway, but also in the MEK and ERK systems in the mTOR pathway.[17]

The LEOPARD acronym serves as a helpful mnemonic device: L, lentigines; E, ECG conduction defects; O, ocular hypertelorism; P, pulmonary stenosis; A, abnormalities of the genitalia; R, retarded growth; and D, deafness.[15] electrocardiogram defects primarily present as left or right ventricular hypertrophy or QT prolongation. From a cardiac standpoint, hypertrophic cardiomyopathy, LEOPARD acronym notwithstanding, is more common than pulmonary stenosis (80% vs 20% of reported cases

Table 2 Mosaic RASopathies

Epidermal nevi and epidermal nevus syndrome	FGF3R or PIK3CA	Mosaicism	Systematized epidermal nevi
Sebaceous nevus and Schimmelpenning syndrome	HRAS or KRAS	Mosaicism	Orange plaque on scalp with associated alopecia
Encephalocraniocutaneous lipomatosis	KRAS	Mosaicism	Café-au-lait macules, hypopigmented macules, epidermal nevi

in the literature).[17,18] Genital abnormalities, particularly cryptorchidism, and short stature occur in over 50% of reported cases with Noonan syndrome with multiple lentigines.[18] Deafness due to sensorineural hearing loss is present in about 20% of reported cases.[18]

Skin findings appear in the first year of life with multiple café-au-lait spots in a generalized distribution.[15] By midchildhood, these patients begin to develop multiple black-brown macule lentigines on the upper part of the body, primarily the facial and upper part of the trunk region.[18] The number of these lentigines continues to increase over time, with the rate of development being highest in the pubertal years, though not with any documented increased risk of cutaneous malignancy. Notably, these patients have been found to have a higher risk of developing medulloblastoma and neuroblastoma, secondary to dysregulation of growth and development signaling pathways

Costello syndrome

Costello syndrome results from an autosomal dominant gain-of-function mutation in the *HRAS* gene. *HRAS*, a protein regulator of cell growth and replication, is directly coded for by this gene, and as such, the gain-of-function mutation leads to reduction in regulation of growth and replication.[7,19,20] Similar to Noonan syndrome with multiple lentigines, Costello syndrome is a rare disease with an estimated prevalence, ranging from 1-in-300,000 to 1-in-1.25 million.[19] The reported number of Costello syndrome cases in the current literature approached 200.

Costello syndrome is characterized universally by developmental delay. Characteristic facial features, including coarse facies (97% of case reports), epicanthal folds (82%), and macrocephaly (84%), are seen in most patients.[21] Patients with Costello syndrome likewise have musculoskeletal and cardiac findings, including hyperextensible joints (primarily the fingers [87%]) scoliosis,[21] hypertrophic cardiomyopathy (61%), and arrhythmias (53%).[21,22]

Patients with Costello syndrome are at greater risk of malignancy, including abdominal and pelvic rhabdomyosarcoma in their childhood years, as well as ganglioneuroblastoma, and, less often, bladder carcinoma. This is consistent with a mutation in a cell growth and replication regulator gene, such as *HRAS*.

A striking cutaneous feature of Costello cutis laxa (99% primarily of the neck, palms, fingers, and soles[21]) includes associated hyperpigmentation (76%).[21] Palmoplantar hyperkeratosis is common, and distinctive centrofacial and perioral papillomas develop with age.

Cardiofaciocutaneous syndrome

Cardiofaciocutaneous syndrome (CFC) is characterized by autosomal dominant activating mutations in various genes, with the most common mutations being in the *BRAF* gene (75-80%) or *MAP2K1/2* gene (10-15%).[23] All three of these respective gene products are part of the RAS/MAPK regulatory pathway, affecting proliferation, differentiation, and apoptosis.[23]

Cardiac anomalies include most commonly pulmonic stenosis and atrial septal defects.[24] Hypertrophic cardiomyopathy is less common. Dysmorphic facial features include ocular hypertelorism, high foreheads, down-slanting palpebral fissures, and macrocephaly.[24] Patients with CFC tend to have coarser facies than patients with Noonan syndrome, but these features are not as course as those seen in Costello syndrome. Neurocognitive developmental delay is nearly universal. CFC are at greater risk for all of these characteristics.[25,26]

Patients with CFC have dystrophic flat nails and sparse, thin eyebrows and eyelashes.[23] Hyperkeratosis on the arms and legs is common, as well as on the palms and soles, as is generalized keratosis pilaris. Severe xerosis and hyperpigmentation, including café-au-lait macules or lentigines, can be seen, though less commonly compared with Costello syndrome.[23,27]

Neurofibromatosis type 1 (aka Von Recklinghausen disease)

Neurofibromatosis type 1 (NF-1) is a common autosomal dominant RASopathy with an incidence estimated at 1-in-2600 to 1-in-3000; approximately half of these cases are familial and the other half *de novo* mutations.[28] NF-1 is caused by a germline microdeletion in the *NF-1* gene at 17q11.2.[29] This gene code is for the protein neurofibromin, a negative regulator of the Ras/MAPK pathway. Neurofibromin catalyzes Ras GTPase activity, thereby inactivating the Ras transduction pathway[30] and resulting in downstream overexpression of mTOR, MAPK, and c-kit. Diagnostic criteria include cutaneous and extracutaneous features, as well as family history.

Café-au-lait macules of sufficient size and number are the hallmark cutaneous feature. Whereas six or more are considered a necessary threshold, any infant with four or more café-au-lait macules should be evaluated. A size distinction is made to discriminate from solar-induced lentigines: >5 mm in a child and 15 mm in an adult. Axillary and inguinal freckling (Crowe sign) may be present at birth or present in the first years of life. Although cutaneous neurofibromas do not usually present until adolescence or beyond, plexiform neurofibromas are thought to be congenital. These lesions are generally larger and appear like an atypical cafe au lait macule, sometimes with associated hypertrichosis, induration, and pruritus. Neurofibromas are benign, peripheral tumors of Schwan cells but can become malignant (malignant peripheral nerve sheath tumors) (Figure 1). Cafe au lait macules tend to increase in number as patients age, before stabilizing after teenage years.[28]

Extracutaneous manifestations include iris hamartomas (Lisch nodules), optic pathway gliomas, and osseous

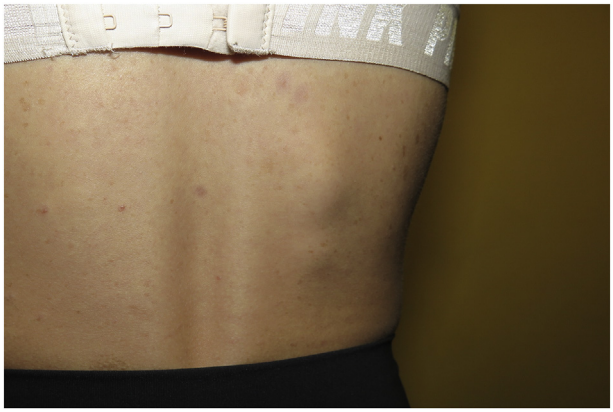

Fig. 1 Neurofibromas on the lower back presenting as slowly enlarging, rubbery, flesh-colored nodules in a patient with neurofibromatosis type 1.

dysplasia.[31] Optic pathway gliomas tend to occur in about 15% of children, usually before the age of 6 years but are rarely symptomatic.[28] Osseus dysplasia tends to occur primarily as bowing of the tibia or pseudarthrosis of a joint after a long bone fracture.[29] These patients also tend to have learning disabilities and suffer from higher rates of scoliosis.

Legius syndrome (NF-1-like syndrome)

Legius syndrome is a RASopathy due to an autosomal dominant gain-of-function mutation in the *SPRED1* gene at 15q14[32] that occurs in roughly 1 in 200,000 individuals. The Spred-1 protein coded for by this gene regulates the Ras/MAPK pathway by binding to Raf, an important intermediary in the signal transduction sequence.[33] *SPRED1* mutations lead to decreased negative regulation of the pathway, thereby promoting proliferation, differentiation, and apoptosis. There are striking clinical similarities to NF-1, and a recent study found that 1.3% of patients diagnosed with NF-1 actually had a *SPRED1* mutation.[34]

Legius syndrome presents with macrocephaly, coarse facies, short statures, and less commonly pectus excavatum/carinatum.[32] Patients with Legius syndrome tend not to have neurocognitive delay but can have ADD or ADHD.[35] Such patients may have café-au-lait spots with intertriginous freckling as in NF-1.

SPRED1 mutation testing is the most conclusive diagnostic method to discriminate Legius syndrome from NF-1.[32]

Mosaic RASopathies

Mosaicism is defined by the presence of two phenotypically distinct cell populations in a single individual due to a postzygotic mutation.[36] The clinical phenotype depends on the specific mutation, timing during development, and the tissue types affected. The recent literature has shown that both organoid and nonorganoid epidermal nevi are caused by mosaic populations of mutated *RAS* proteins.[36] There is no general consensus on the type and intensity of cancer screening indicated in patients with mosaic RASopathies, but case reports continue to suggest the importance of such awareness. A recently described patient had phakomatosis pigmentokeratotica due to a mosaic *HRAS* mutation and subsequently developed rhabdomyosarcoma.[37] The cutaneous expression of mosaic *RAS* mutations can be melanocytic or nonmelanocytic lineages.[38]

Epidermal nevi and epidermal nevus syndrome

Epidermal nevi are common examples of cutaneous mosaicism.[39] These typically congenital, linear, localized plaques present in lines of Blaschko and have a benign natural history. Mosaic mutations in several genes have been identified including, *FGF3R* and *PIK3CA*.[2,3] A recent report of a series of 72 patients with epidermal nevi showed that 39% had *RAS* mutations.[40] Mutations in either *HRAS*, *KRAS*, or *NRAS* were found, coincident in some patients with *PIK3CA* mutations but exclusive of *FGF3R* mutations. Extensive cutaneous involvement, often called "systematized epidermal nevi" or "ichthyosis hystrix," have also been associated with similar mutations presumably occurring earlier in development When these patients have associated neurologic, musculoskeletal, cardiac, or renal anomalies, they have been labeled as having epidermal nevus syndrome.[41]

The oncologic implications of a mosaic *RAS* mutation are uncertain; however, more extensive cutaneous involvement should prompt greater concern for extracutaneous abnormalities, including malignancy. A 6-month-old infant has been reported with a keratinocytic epidermal nevus, polycystic kidneys, growth retardation, and rhabdomyosarcoma in the setting of a *KRAS* G12D mutation.[42] There has been a similar patient with a systematized epidermal nevus, urogenital cancer, and an oncogenic *HRAS* mutation.[40]

Sebaceous nevus and Schimmelpenning syndrome

Nevus sebaceous is a postzygotic mosaic RASopathies, secondary to an activating mutation in the *HRAS* or *KRAS* gene, leading to cell growth secondary to activation of the MAPK signal-transduction pathway.[43,44] The occurrence in most of these patients tends to be sporadic, and the incidence is approximately 0.3% of newborns.

Clinically, patients with nevus sebaceous are born with 1- to 4-cm, thin, yellow-organ linear plaques, primarily on the scalp with an associated area of alopecia.[45] These lesions can become elevated or nodular, when such patients undergo puberty, presumed to be secondary to hormonal influence.

These patients are at an increased risk of epithelial cancers, both benign and malignant. Benign tumors include trichoblastomas, sebaceomas, and nodular hidradenomas, whereas malignant neoplasms include basal cell carcinomas,

apocrine carcinomas, and sebaceous carcinomas.[46] The reported risk of epidermal malignancies has ranged from 8% to 16% in various studies, with the rate of secondary neoplasms being as high as 22.5%.

The histopathology of the epidermis in these patients shows acanthosis and papillomatosis, and the pathognomonic finding for this disease is multiple immature hair follicles.[46] The pathology also often shows an increased prevalence of sebaceous and ectopic apocrine glands.

Nevus sebaceous syndrome (also known as Schimmelpenning syndrome) is the presence of linear nevus sebaceous spread in a pattern along the lines of Blaschko in addition to having cerebral or skeletal defects.[47] Patients can present with mental retardation, seizures, or ocular colobomas.[43] The genetics of Schimmelpenning syndrome are thought to occur secondary to more serious *HRAS* or *KRAS* gene mutations and for that reason hypothesized to only be viable in the form of somatic mosaicism as nonmosaic cases would be lethal.[48] There is a report of a 6-year-old with Schimmelpenning syndrome due to a postzygotic *KRAS* G12D mutation who also had renovascular hypertension, diabetes mellitus, and congenital lipomatosis.[49]

Encephalocraniocutaneous lipomatosis

Encephalocraniocutaneous lipomatosis is characterized by an alopecic fatty nevus in the scalp (nevus psiloparus), ocular abnormalities, and neurologic disturbance including seizure disorder, developmental delay, and central nervous system tumors. A mosaic *KRAS* mutation has been identified in four patients with encephalocraniocutaneous lipomatosis.[50] There is also a report of a 5-year-old with encephalocraniocutaneous lipomatosis and a progressive pilocytic astrocytoma, refractory to standard chemotherapy. The child was stabilized after the identification of an *FGR* mutation and initiation of the *MEK* inhibitor trematinib.[51]

Dermatology residents are taught to risk-assess infants with certain birthmarks, including café-au-lait macules and hypopigmented macules, as they may herald medical risk. It would seem prudent in light of current knowledge of RAS mutations and cancer predisposition that epidermal nevi are likewise afforded such scrutiny.

Emerging RASopathies

CM-AVM RASA1/RASA2 (CM-AVM)

The genetic disease caused by the *RASA1* mutation is known as the capillary malformation–arteriovenous malformation (CM-AVM) syndrome. This disease is characterized, as the name implies, by a disorder of the vascular system, causing the formation of capillary and arteriovenous malformations both in the skin and in the viscera.[52] Genetically, the disactivating mutation in the *RASA1* gene leads to a nonfunctioning protein product p120-*RasGAP*, a regulator of the Ras-GTP signal transduction pathway.[52–54] As such, this defective protein product leads to a removal of the negative regulation of this signaling pathway. The penetrance of CM-AVM is 90% to 99%, and the prevalence is estimated by 1:100,000 in Northern Europeans.[52]

Clinically, the AVM part of CM-AVM, with 15% to 20% of patients developing an AVM, can lead to the production of arteriovenous malformations and fistulas, both of which can lead to abnormal bleeding, migraines and seizures (from intracranial AVMs/Arteriovenous fistulas), and even high-output heart failure (secondary to decreased end-organ perfusion from new low-resistant circuits created by AVMs).[53]

Capillary malformations (also known as "port-wine stains") primarily present as multiple, pink, 1- to 2-cm, round lesions with a white halo localized primarily to the face and limbs[54,55] (Figure 2).

These capillary malformations are caused by the capillary malformations in the papillary dermis reflecting light off the skin. They can interestingly be visualized by arterial Doppler when the etiology is in question.

Diagnostic technologies

The primary means of diagnosing RASopathies is through genomic DNA analysis, using specific gene sequencing.[56] A common method includes procuring DNA from circulating leukocytes and using denaturing high-performance liquid chromatography to examine for single-strand polymorphisms in the exons and flanking intron regions of the genes of interest.[56,57] Recently next-generation sequencing, including multigene sequencing panels, whole-exome sequencing, and whole-genome sequencing, has been employed for a more granular search for mutations.[58–60]

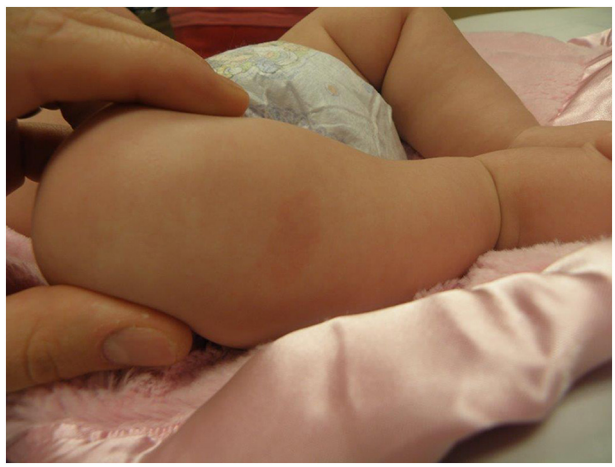

Fig. 2 Blanchable pink patch with a peripheral halo in a patient with capillary malformation–arteriovenous malformation syndrome due to *RASA1* mutation.

Gene panel probing for specific mutations continues to the most commonly used means of testing in clinical laboratories. In many situations, it is both more economical and more clinically sensitive than whole-genome sequencing.[58,60]

Therapeutic implications

There are potential therapeutic implications for the discovery of numerous genetic pathways of RASopathies. Many new treatments targeting the Ras/MAPK pathway have recently been designed as inhibitors in oncology for cancer management.[57] As all RASopathies fundamentally derive from a malfunction of the Ras system, potential targeting of these pathways with specific molecular treatments holds great promise; however, significant questions remain about the implications of treating a mosaic disease with systemic options and the potential side effects such regimens may have.

As of 2018, limited small-molecular treatments have been used in RASopathies to see their potential benefit. Primarily, current targets for treatment are focused on neurocognitive components, as it provides a focused target system to which more local delivery can be applied.[57]

Trials using simvastatin or lovastatin were thought to be of promise, as statins interfere with the cholesterol synthesis pathway, the same pathway from which Ras isoprenylation is derived, an important contributor to Ras activity.[61] Unfortunately, both trials have been largely unsuccessful with no detectable impact on neurocognitive development despite changes on functional MRI.[61,62]

A more recent trial involved testing an *MEK* inhibitor *MEK*162 to determine its impact on the left ventricular mass in children with Hypertrophic obstructive cardiomyopathy.[57] There is hope that Costello syndrome and CFC can be treated with such a medication due to their *HRAS* mutation, which allows them to be directly targeted by farnesyl transferase inhibitors.[63]

Conclusions

Café-au-lait macules and lentigines have historically triggered consideration of a discrete set of conditions, most notably NF-1. Clinicians should not abandon their hard-wired scrutiny of these specific conditions; however, this review highlights the broader considerations related to mutations in the MAP/Ras pathway. Prompt, appropriate diagnosis is essential, as some of these conditions can have neurodevelopmental implications early in life and potential malignancy risk later.

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