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Tegumentary manifestations of Noonan and Noonan-related syndromes

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OBJECTIVES: Noonan and Noonan-related syndromes are common autosomal dominant disorders with neuro-cardio-facial-cutaneous and developmental involvement. The objective of this article is to describe the most relevant tegumentary findings in a cohort of 41 patients with Noonan or Noonan-related syndromes and to detail certain aspects of the molecular mechanisms underlying ectodermal involvement.

METHODS: A standard questionnaire was administered. A focused physical examination and a systematic review of clinical records was performed on all patients to verify the presence of tegumentary alterations. The molecular analysis of this cohort included sequencing of the following genes in all patients: *PTPN1*, *SOS1*, *RAF1*, *KRAS*, *SHOC2* and *BRAF*.

RESULTS: The most frequent tegumentary alterations were xeroderma (46%), photosensitivity (29%), excessive hair loss (24%), recurrent oral ulcers (22%), curly hair (20%), nevi (17%), markedly increased palmar and plantar creases (12%), follicular hyperkeratosis (12%), palmoplantar hyperkeratosis (10%), café-au-lait spots (10%) and sparse eyebrows (7%). Patients with mutations in *PTPN11* had lower frequencies of palmar and plantar creases and palmar/plantar hyperkeratosis compared with the other patients.

CONCLUSIONS: We observed that patients with mutations in genes directly involved in cell proliferation kinase cascades (*SOS1*, *BRAF*, *KRAS* and *RAF1*) had a higher frequency of hyperkeratotic lesions compared with patients with mutations in genes that have a more complex interaction with and modulation of cell proliferation kinase cascades (*PTPN11*).

KEYWORDS: Noonan; Skin; Tegument; Tegumentary.

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INTRODUCTION

Noonan syndrome (NS; Online Mendelian Inheritance in Man [OMIM] 163950) and Noonan-related syndromes (NRS), such as cardiofaciocutaneous (CFC) syndrome (OMIM 115150), NS with multiple lentigines (NSML]; OMIM 151100), Costello syndrome (CS; OMIM 218040), neurofibromatosis type I (NFI; OMIM 162200), Legius syndrome (LS; OMIM 611431) and NS with loose anagen hair (NSLAH; OMIM 607721) are common autosomal dominant disorders with neuro-cardio-facial-cutaneous and developmental involvement. These syndromes share common traits, such as craniofacial dysmorphisms, short stature, cardiac malformations, variable cognitive impairment, an increased risk of cancer development and a certain extent of tegumentary involvement (1).

These disorders are caused by germline mutations in genes that participate in the rat sarcoma/mitogen-activated protein kinase (RAS/MAPK) pathway, which transduces extracellular growth factor signals into the intracellular environment and plays a role in cell cycle regulation, differentiation, growth and death and affects the inflammatory response (2,3). Although the role of the RAS/MAPK pathway in skin development and functioning is not completely understood, several skin manifestations in individuals with NS and NRS have been described, such as pigmented lesions (café-au-lait [CAL] spots, lentigines and melanocytic lesions), proliferative ectodermal lesions (e.g., ichthyosiform manifestations, follicular hyperkeratosis, and short, curly and thin hair) and hyperplasia (redundant skin and papillomatous growths) (1,4). Several of these skin manifestations are associated with a specific

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syndromic phenotype, such as lentigines in NSML patients, thin, sparse hair in NSLAH patients and hyperkeratotic skin in CFC syndrome and in NS patients harboring *SOS1* gene mutations (1). The exact underlying molecular mechanism determining the diverse physiopathological spectrum of lesions, the association of specific tegumentary lesions with specific syndromes and the increased prevalence of tegumentary involvement in groups with mutations in specific genes is still unknown (1,5-7).

The exact delineation of the tegumentary findings in each group of patients harboring mutations in different genes, a comprehensive genotype-phenotype correlation in NS and NRS patients and a model of the molecular mechanisms of the diseases all remain to be determined.

The objective of this article is to describe the most relevant tegumentary findings in a cohort of 41 patients with NS or NRS who harbor a confirmed germline mutation in genes of the RAS/MAPK pathway and to unveil certain aspects of the molecular mechanisms underlying ectodermal involvement in NS and NRS patients by comparing the clinical features of patient groups classified by their gene mutations.

MATERIALS AND METHODS

A prospective study that included 41 patients affected by NS or NRS was performed at the Outpatient Clinic of the Genetics Unit of Instituto da Criança do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. The majority of these patients were referred to our unit by pediatric endocrinology and cardiology services. Consensus clinical criteria were used to classify the patients as being affected by NS, NSML or CFC syndrome (8-11). Only one patient, who had tested negative for the previously described gene alterations in other known NS-related genes (*PTPN11*, *SOS1*, *RAF1* and *KRAS*), was diagnosed with NSLAH by the presence of slow growth, fine hair and a *SHOC2* gene mutation (p.S2G). Another patient, who presented with the mutation p.T468M in the *PTPN11* gene, which is usually associated with NSML, was classified as an NS patient because he lacked lentigines by the age of 21 years.

The molecular analysis of this cohort included the sequencing of the following genes in all patients: *PTPN11*, *SOS1*, *RAF1*, *KRAS* and *SHOC2*. Additionally, the *BRAF* gene was analyzed in patients fulfilling CFC syndrome diagnostic criteria. The p.T470P (*BRAF* gene) gene alteration was novel; in silico prediction (PolyPhen, SIFT and Mutation Taster) suggested that the mutation damaged the protein structure and affected protein function, indicating the alteration's pathogenicity. The mutation was a *de novo* event in the family.

A standard questionnaire was administered, and a focused physical examination based on a systematic review of clinical records was performed on all patients to verify the presence of the following complaints: xeroderma (the presence of dry skin, indicated by either scaling or cracking of the skin upon clinical examination), photosensitivity (a subjective impression of greater skin redness following sun exposure), hair loss (a subjective sensation of thinning of the hair), lentigines (the presence of >100 lentiginous lesions), CAL spots (uniformly light brown, sharply defined and usually oval-shaped skin patches), thin hair, curly hair, sparse eyebrows, a clinical history of recurrent oral ulcers, nevi (at least 100), hyperpigmentation of the skin (increased pigmentation of the skin compared with other family members), cutis marmorata (a reticulated cutaneous vascular pattern with altered color (red or blue), follicular hyperkeratosis, palmo-plantar hyperkeratosis (the presence of areas of thickening of the skin in the palmar and plantar regions), markedly increased palmar and plantar creases, keloid scars (excessive growth of scar tissue), nasal papilloma (cauliflower-like epithelial lesions) and the early onset of gray hair. The presence or absence of subjective clinical signs was based on the clinical impression of the genetic unit team, which is experienced when evaluating patients with NS and NRS. Therefore, the clinical protocol and physical examination were applied using the same clinical criteria for all patients.

Statistical analyses comparing the between-group differences, which were stratified by age, gender and gene mutation, were performed using Fisher's exact test with a significance limit of 0.05. The Student's t-test was used to compare the frequency distribution of tegumentary findings between a group of patients with mutations in *PTPN11* and a group that comprised the remaining individuals. The samples did not show any deviation related to gender or age, indicating that sample bias was unlikely.

Ethics

The local ethics committee (Comissão de Ética para Análise de Projetos de Pesquisa [CAPPesq] do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - 0843/08 and 0325/10) approved this study, and written informed consent was obtained from all participants.

RESULTS

Patients ranged in age from five to 58 years, with a mean age of 20 years and a median age of 17 years. Gender was almost equally distributed (21 females and 20 males). The cohort was composed of 36 NS patients, two CFC syndrome patients, two NSML patients and one NSLAH patient. The molecular analysis identified 30 patients harboring mutations in *PTPN11*, five in *SOS1*, two in *BRAF*, two in *RAF1*, one in *SHOC2* and one in *KRAS*. Most individuals (34 patients, 83%) were sporadic cases caused by a *de novo* mutation, whereas familiar aggregation was found in seven patients (three individuals in one family and two individuals in each of two families).

The following tegumentary alterations were observed, in order of prevalence: xeroderma (46%), photosensitivity (29%), excessive hair loss (24%), recurrent oral ulcers (22%), curly hair (29%), nevi (20%), follicular hyperkeratosis (17%), markedly increased palmar and plantar creases (15%), CAL spots (15%), sparse eyebrows (12%), palmo-plantar hyperkeratosis (10%), lentigines (5%), keloid scars (5%), hyperpigmentation of the skin (5%), nasal papilloma (2%), the early onset of gray hair (2%), cutis marmorata (2%) and thin hair (2%). The great majority of individuals (93%) presented with at least one tegumentary involvement (mean of three, median of two, maximum of nine), whereas three individuals did not present with any tegumentary involvement. The most relevant clinical characteristics of these patients are summarized in Table 1 and shown in Figure 1.

The mean number of positive tegumentary findings was highest in the group of patients with CFC syndrome (n = 6 findings/individual), followed by NSML (n = 5), NSLAH

Table 1 - Genetic and clinical profiles of the 41 patients diagnosed with Noonan syndrome and Noonan-related syndromes. The syndrome column shows the clinical diagnosis of the patients; the gene column contains each gene; the mutation column contains the pathogenic alteration in the product of the genes; and the clinical characteristics column shows the most relevant clinical features of each patient, including age and gender, and tegumentary involvement is in brackets. Note that patients with no tegumentary involvement are indicated in bold.

Syndrome	Gene	Mutation	Clinical characteristics
NS	*PTPN11*	p.G60A	29 yo Male (OU; N; CAL; GH)
		p.Y62D	24 yo Male (Xe; N; CAL)
		p.Y63C	9 yo Male (P; PH; FH) ǀ 9 yo Female (Xe; OU) ǀ 11 yo Male (Xe)
		p.Q79R	23 yo Female (CM) ǀ 19 yo Male (Xe; P; OU)
		p.D106A	10 yo Female (SE)
		p.I282V	12 yo Male (Xe)
		p.F285S	33 yo Female (Xe; P; HL; Cr; FH; CH; SE)
		p.N308D	**13 yo Female** ǀ 17 yo Female (CH; FH) ǀ 22 yo Male (Xe; P; OU; CH) ǀ 56 yo Male (HL) ǀ 11 yo Female (Xe; P; OU) ǀ 12 yo Male (N) ǀ 21 yo Female (Xe; HL) ǀ 5 yo Female (CH; SE) ǀ 20 yo Male (Xe)
		p.N308S	**29 yo Male** ǀ **56 yo Female** ǀ 16 yo Female (HL; Ke) ǀ 32 yo Female (CH; P; N) ǀ 15 yo Female (HL; N; Ke) ǀ 11 yo Male (Xe; CH)
		p.T468M	21 yo Male (N; CAL; Cr)
		p.M504V	12 yo Male (P; OU)
		p.Q510P	8 yo Male (CH; CAL)
	RAF1	p.P235S	12 yo Female (PH)
		p.S257K	8 yo Male (N)
	SOS1	p.M269T	27 yo Male (Xe; P; CH; Cr; FH; HS) ǀ 58 yo Female (Xe; HL) ǀ 7 yo Male (Cr)
		p.R552G	28 yo Female (P; Cr; FH; CH)
		p.R552S	13 yo Male (CAL)
	KRAS	p.K5E	24 yo Female (Xe; HL; OU; CH; Cr; FH; HS; NP; Ly)
CFC	*BRAF*	p.N581D	17 yo Female (Xe; P; CH; FH; PH; SE)
		p.T470P	9 yo Female (Xe; HL; CH; N; PH; SE)
NSML	*PTPN11*	p.Y279C	31 yo Female (Xe; P; CAL; Le) ǀ 18 yo Female (Xe; P; HL; OU; Le)
NSLAH	*SHOC2*	p.S2G	40yo Male (Xe; HL; OU; TH)

Xe: xeroderma, P: photosensitivity, HL: excessive hair loss, OU: recurrent oral ulcers, CH: curly hair, N: nevus, Cr: markedly increased palmar and plantar creases, FH: follicular hyperkeratosis, PH: palmo-plantar hyperkeratosis, CAL: café-au-lait spots, SE: sparse eyebrows, Le: lentigines, Ke: keloid scars, HS: hyperpigmentation of the skin, NP: nasal papilloma, GH: the early onset of gray hair, CM: cutis marmorata, TH: thin hair.

(n = 4) and NS (n = 2). When we stratified the patients by the affected gene, the ranking of the mean number of positive tegumentary findings per individual in each group was as follows: *KRAS* (n = 9 findings/individual), BRAF (n = 6), *SHOC2* (n = 4), *PTPN11* (n = 3), *SOS1* (n = 2) and *RAF1* (n = 1).

The distribution of the number of tegumentary findings in patients harboring *PTPN11* mutations (mean = 1.9, standard deviation [SD] = 1.42) compared with patients with mutations in other genes (mean = 3.6, SD = 2.6) showed a significant difference ($p = 0.0352$).

CAL spots were more common in males ($p = 0.0471$). Follicular hyperkeratosis was statistically more prevalent in postpubertal (>16 years of age) patients ($p = 0.0269$). No patients harboring a *PTPN11* mutation developed a nevus prior to the age of 11 years in contrast to patients harboring other gene mutations ($p = 0.0476$).

Patients with *PTPN11* mutations had a lower frequency of follicular hyperkeratosis (3.5% *vs.* 40%, $p = 0.011$) and markedly increased palmar and plantar creases (3.5% *vs.* 40%, $p = 0.011$) and palmar/plantar hyperkeratosis (3.5% *vs.* 30%, $p = 0.0449$) compared with other patients. Comparing the *PTPN11* patients with the *SOS1* patients, the *PTPN11* patients had a lower frequency of follicular hyperkeratosis (3.5% *vs.* 50%, $p = 0.0326$) and markedly increased palmar and plantar creases (3.5% *vs.* 75%, $p = 0.0029$).

DISCUSSION

In the current study, we described the most relevant tegumentary findings in a cohort of 41 patients with a molecularly proven diagnosis of NS or NRS. We found that these tegumentary findings are common in these syndromes, particularly in patients with *BRAF*, *KRAS* and *SHOC2* mutations. Note that this phenomenon was demonstrated in a sample composed of mostly young individuals. This report is the first comprehensive study in the literature to address tegumentary involvement in NS patients with germline mutations in several genes of the RAS/MAPK pathway. Several of the manifestations reported in this article have not been previously described in the literature, including the frequency of tegumentary involvement in this syndromic group as a whole.

The association of CAL spots with male gender is not exclusive to our group of patients because CAL spots are more commonly observed in normal males than in normal females (12). We also observed that follicular hyperkeratosis and nevi are associated with postpubertal age, which we speculate is because of an accumulation of sun exposure or hormonal influence.

The RAS/MAPK signaling pathway receives extracellular stimuli from cell surface receptors and acts as a molecular switch in the processes of cell proliferation, differentiation, survival and death (13). Several components of this pathway are related to the promotion of epidermal proliferation and may interfere in the epidermal cell state (4,14). Signal transmission is initiated by the extracellular stimulators (growth factors, hormones and cytokines) that create intracellular docking sites for adaptor molecules activating cell surface receptors. This interaction promotes the activation of RAS GTPases, including the products of *KRAS*, *NRAS* and *HRAS* (monomeric GTPases that use GDP/GTP-regulated molecular switching to control intracellular signal

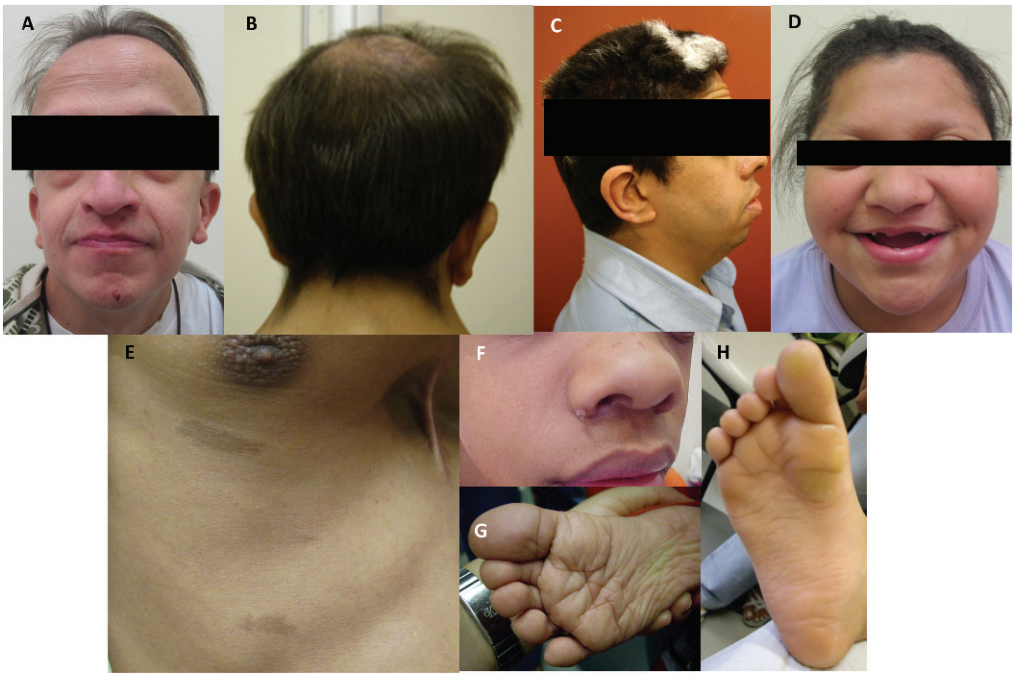

Figure 1 - Mosaic showing several tegumentary findings of the patients reported in this article. **A and B)** A patient with Noonan syndrome with loose anagen hair and SHOC2 mutation (p.S2G) who presented with thin hair and premature baldness; **C)** a patient with Noonan syndrome and PTPN11 (p.G60A) mutation with premature graying of the hair; **D)** a patient with CFC syndrome (*BRAF* p.N581D), sparse eyebrows and follicular hyperkeratosis; **E)** a patient with Noonan syndrome (PTPN11 p.T468 M) who presented with café-au-lait spots and prominent pectus excavatum; **F and G)** a patient with Noonan syndrome (KRAS p.K5E), nasal papillomas and marked plantar creases; 1H: a patient with CFC syndrome (BRAF p.T470P) and plantar hyperkeratosis.

flow), and, therefore, the interaction and activation of the RAF protein kinase components, including the products of *RAF1* and *BRAF*, members of a small family of serine-threonine kinases that function as RAS effectors. Activating the RAF cascade results in the phosphorylation and activation of the final MAPK components (the substrates of the pathway) and, consequently, cellular responses (1,4,13,14).

The *PTPN11* gene encodes SHP2, a cytoplasmic protein tyrosine phosphatase that positively modulates RAS signaling through its interaction with the GRB2/SOS1 complex. SHP2 also exhibits other intricate, contradictory and relatively unknown interactions. *SOS1* encodes a multidomain product that catalyzes the release of GDP from RAS through a close interaction with GRB2. This event facilitates the conversion of the inactive form of RAS into its active GTP-bound state. The *SHOC2* gene encodes a protein that positively modulates the RAS-MAPK signal flow (1,4,14,15). Interestingly, *PTPN11* is the only studied gene that also functions as a downregulator (unlike *SOS1*, *KRAS*, *RAF1* and *BRAF*) (National Cancer Institute, Pathway Interaction Database, USA). For example, *PTPN11* specifically inhibits the GRB2/SOS1 complex in the neuromuscular junction (16).

We observed that patients with mutations in genes directly involved in the kinase cascades for cell proliferation (*SOS1*, *BRAF*, *KRAS* and *RAF1*) have a higher frequency of proliferative skin lesions (hyperkeratosis and marked palmar and plantar creases) compared with patients with mutations in a gene that has a more complex interaction with and modulation of this transduction pathway (*PTPN11*). Previous studies have also supported this observation. Hyperkeratosis has been described in patients harboring mutations in those genes. Additionally, patients with mutations in *MEK1* and *MEK2*, the final effectors of the MAPK cascade, develop remarkable tegumentary involvement that usually includes hyperkeratosis (7). Activation of the RAS/MAPK pathway by a contradictory effect of dabrafenib, a *BRAF* inhibitor used to treat melanoma, induces the proliferation of keratinocytes and predisposes patients to hyperkeratosis (17).

Limitations of this study include the descriptive nature of the data and the relatively small sample size for statistical analysis, although a sample size of 41 is considerable for rare genetic disorders. Additionally, several tegumentary findings described here (i.e., xeroderma and photosensitivity) are either common in the normal population or are diagnosed solely based on patient complaints or the clinical impression of the examiner; therefore, the prevalence of these conditions in our patients may have been inflated. Despite our work to improve the delineation of tegumentary genotype-phenotype correlations in this study, we encourage further investigation in this field.

A thorough description of dermatological findings has been developed for Costello syndrome, an NRS caused by germline mutations in *HRAS* (5). Costello syndrome patients have a statistically higher frequency of cutaneous papillomas and palmar hyperkeratosis but a lower frequency of sparse eyebrows compared with patients with CFC syndrome (i.e., harboring mutations in *BRAF*). Although our study did not include patients with Costello syndrome or any patients with *HRAS* mutations, one patient with a *KRAS* mutation presented with nasal papilloma and other characteristics that overlap with the characteristics observed in Costello syndrome, such as distal hyperextensibility, marked palmar creases and facial dysmorphisms (18). As this patient

presented with several tegumentary findings and was the only one harboring a *KRAS* mutation, we may have overestimated the prevalence of skin abnormalities in patients with this gene mutation.

Cutaneous manifestations in patients with *BRAF* mutations (i.e., mainly patients with CFC syndrome) have also been reported, with a high frequency of melanocytic nevi, hyperkeratosis of the palms and soles (typically developed in pressure areas) and follicular hyperkeratosis (6).

Tegumentary involvement in NS and NRS patients was common, even in a sample composed of mostly young individuals. Therefore, an active search for cutaneous involvement in NS and NRS patients and the addition of dermatologists to the multidisciplinary team required to assist these patients is necessary for optimal follow-up treatment. Clinicians must keep in mind that several of these skin lesions could have a late onset and thus hinder a straight genotype-phenotype correlation.

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■ AUTHOR CONTRIBUTIONS

Quaio CR, Almeida TF, AAL Jorge, AC Malaquias, Kim CA and Bertola DR designed the study and were responsible for the patient data collection, manuscript writing and review. Almeida TF was also responsible for the statistical analysis. Brasil AS and Pereira AC performed the molecular analysis and reviewed the manuscript.

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