Familiar acanthosis nigricans and FGFR3 mutations: spectrum of pediatric presentations in two different families

David Pesqué[1], Álvaro March-Rodriguez[1], Irene Abreu-Rodríguez[2], Luis A Pérez-Jurado[2], Ramon M Pujol[1]

1. Department of Dermatology. Hospital del Mar (Barcelona, Spain)
2. Department of Genetics. Hospital del Mar (Barcelona, Spain)

Introduction

Isolated (non-syndromic, non-endocrinopathy) Familial Acanthosis Nigricans (FAN) has been occasionally depicted.[1] FGFR3 mutations have been related to FAN associated to skeletal disorders, and only rarely has FAN, related to FGFR3 mutation(s) and without skeletal dysplasia, been described.[2,3] We present two families with isolated FAN due to different mutations of FGFR3, with the pediatric clinical and genetic characterization.

Clinical case

Family 1: A 5-year-old girl consulted for progressive velvety hyperpigmentation in the perioral and perinasal region (Figure 1A). The mother (35yo) referred also perioral hyperpigmentation at an early age with posterior extension to cervical folds. This clinical picture was also present in the grandmother (60yo). No other remarkable clinical or exploratory findings were noted.

Family 2: A 15-year-old girl consulted for a clinical picture of recent-onset subtle abdominal (Figure 1B) and axillary hyperpigmentation (Figure 1C). In addition, she had presented with perioral hyperpigmentation since early childhood. Her mother (48yo) and her aunt (43yo) had also presented with similar clinical pictures, with the later associating also early onset seborrheic keratoses (SK) (Figure 1D).

Complementary tests: For both families laboratory and endocrine exams were normal. Their height, head size, shape, and body proportions were normal. Skin biopsies disclosed acanthosis, papillomatosis, basal cell layer hyperpigmentation, suggesting the diagnosis of acanthosis nigricans.

Clinical and genetic testing details are presented in Table 1 and Figures 1A-D and 2.

Figure 1. Clinical pictures. A. Perioral and perinasal hyperpigmentation. B. Abdominal hyperpigmentation. C. Axillary hyperpigmentation. D. Multiple abdominal seborrheic keratoses

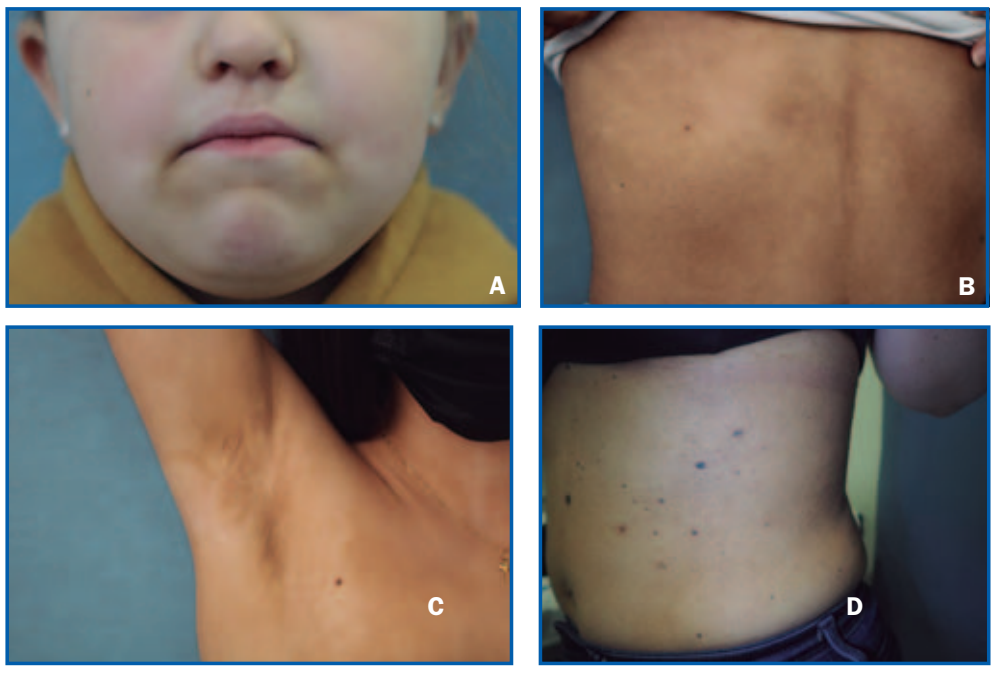

Figure 2. Genetic representation of FGFR3 mutations in the extracellular and intracellular domain of skin disorders with or without skeletal dysplasias and skeletal dysplasias without skin involvement

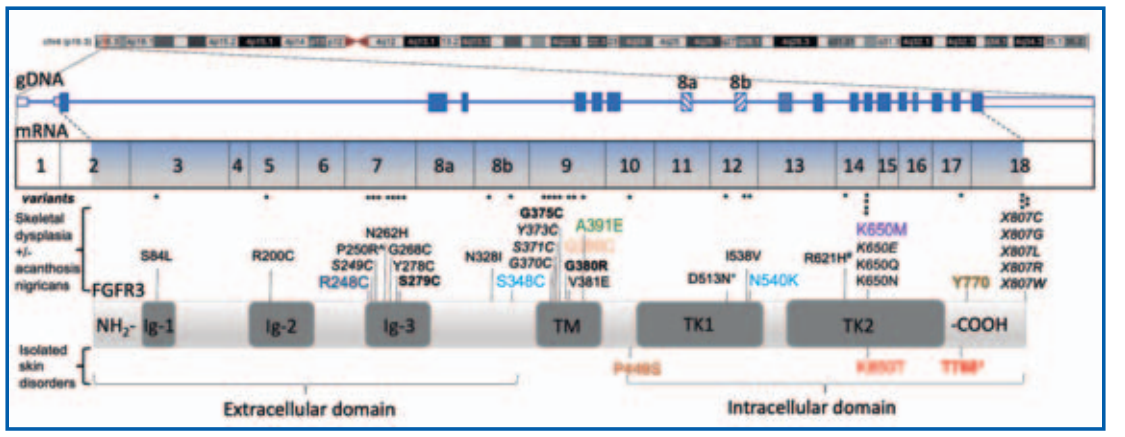

Table 1. Clinical and genetic testing details

Family	Age	Sex	Onset	Initial location	Extension (adolescence)	Extension (adulthood)	Other features	Genetic testing in skin and blood
1	5 yo(*)	W	2 yo	Perioral and perinasal	None	None	None	[redacted] Germline heterozygous nonsense mutation (exon 18)
	35 yo	W	1 yo	Perioral	Cervical (anterior)	Cervical (posterior)	None	
	60 yo	W	<1yo	Perioral	Cervical and axillary folds	Abdominal folds	None	
2	15 yo(*)	W	6m	Perioral	Abdominal and axillary folds	None	None	[redacted] Germline heterozygous missense mutation (exon 14)
	43 yo	W	1yo	Perioral	Cervical (discrete)	Abdominal folds	Early onset SK	
	48 yo	W	1yo	Cervical	None	Abdominal and axillary folds	None	

Table legend: (*)Proband, yo (years-old), SK (sebhorreic keratosis)

Discussion

Clinical features

Despite different genetic background, both families presented with similar clinical findings at an early age (6-24 months): Perioral velvety hyperpigmentation, that could be associated to perinasal hyperpigmentation. During the pediatric period, the hyperpigmentation was subtle with a slow progressive darkening and could have been overlooked at early stages. The clinical picture was stable until the first decade of life when the clinical picture expanded to other anatomic areas. Despite a variable intra and interfamilial evolution, a common pattern of body extension: initially face hyperpigmentation is noted, with subsequent cervical extension in the adolescence, and then variable axillary and/or abdominal affection during adulthood.

Genetics

Family 1: A nonsense germinal FGFR3 mutation in exon 18, only reported in two previous families, was detected. This mutation is predicted to generate a truncated FGFR3 protein that lacks the sixth and last autophosphorylation site located in the C-terminal tyrosine residue (Y770), which is conserved among all FGF receptors (FGFR1–4). Unlike the proximal five phosphorylation sites, it negatively regulates downstream signaling when phosphorylated. The truncated protein, missing only a negative regulator of downstream signaling, may lead to significantly aberrant FGFR3 activity only reaching clinical threshold in keratinocytes.

Family 2: A missense germinal mutation in exon 14 was observed. This mutation is found in a common hotspot that leads to FAN with skeletal disorders. Our precise mutation K650T has been considered to be less effective in the constitutive activation of FGFR3 than K650M or K650E.[4] The 43-year-old women of the Family 2 also presented with childhood-onset generalized SK. The genetic study of the SK revealed the presence of the germline FGFR3 mutation and the presence of a post-zigotic PIK3CA: c.311C>T mutation. Despite this mutation is not among the most common mutation associated to SK,[5] it could be hypothesized that its occurrence with the underlying FGFR3 mutations may lead to the activation of keratinocytes.

Conclusions

The presence of childhood-onset perioral or nasolabial hyperpigmentation, or extensive acanthosis nigricans may justify targeted testing of the FGFR3 gene. Furthermore, considering that, in the absence of insulin resistance and/or other associated syndromic features, acanthosis nigricans can be caused by a few specific variants in a single gene, (targeted) mutation screening of FGFR3 should be included in the diagnostic work-up of any patient with familiar isolated acanthosis nigricans.

References

1- Pesqué D et al. Familial isolated acanthosis nigricans due to a recurrent FGFR3 truncating mutation. Clin Exp Dermatol. 2023 Feb 27:llad078.
2- Tahara U et al. Autosomal dominant familial acanthosis nigricans 10 caused by a C-terminal nonsense mutation of FGFR3. J Hum Genet. 2021; 66:831-834.
3- Yasuda M et al. Familial acanthosis nigricans with the FGFR3 mutation: differences of pigmentation between male and female patients. J Dermatol 2018; 45:1357–61.
4- Bellus GA et al. Distinct missense mutations of the FGFR3 lys650 codon modulate receptor kinase activation and the severity of the skeletal dysplasia phenotype. Am J Hum Genet. 2000;67:1411-21;
5- Hafner C et al. Oncogenic PIK3CA mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern. Proc Natl Acad Sci U S A. 2007;104:13450-4.

Hospital del Mar — Parc de Salut MAR Barcelona