TITLE

Report of a case of RAVEN, hair heterochromia and autism in the setting of FGFR2 mutation

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ABSTRACT

A newborn presented with extensive rounded and velvety epidermal nevus (RAVEN) with a genetic study of the cutaneous lesions revealing a heterozygous mutation in FGFR2 (p.Cys382Arg). At two years-old our patient developed hair heterochromia and autism spectrum disorder. Although RAVEN was initially associated with fibroblast growth factor 3 (FGFR3) mutations, three cases of RAVEN have been identified with mutations in FGFR2 (p.Ser252Trp) and one case of linear keratinocytic epidermal nevi has been identified with the same mutation as the mutation identified in our patient. This strongly supports the pathogenic role of these mutations.

MAIN TEXT

Introduction

Nevoid acanthosis nigricans (AN) or RAVEN (rounded and velvety epidermal naevus) is a very uncommon form of epidermal nevus. It has been linked to mutations in the *FGFR2* and *FGFR3* genes.

Case report

A full-term newborn product of *in vitro* insemination and a twin pregnancy presented with extensive lesions of linear distribution on the left leg, composed of rounded and oval light brown papules and plaques with well-defined borders. After some months the lesions darkened and acquired a velvety texture (Figure 1). Similar lesions also appeared on the right plantar foot, supraumbilical midline, and right scapula. At 2 years of age, hair heterochromia was observed in the parieto-occipital region (Figure 2). The patient also had a language delay and was followed by neurology for autism spectrum disordersince 18 months of age. Cutaneous histology at 6 months of age showed hyperkeratosis with papillomatosis and

acanthosis, without alterations in the dermis or hypodermis (Fig 3). The skin lesion was sequenced with TruSight™ Oncology 500 kit (TSO500; Illumina, San Diego, CA, USA), and a likely pathogenic heterozygous gain-of-function mutation was detected in *FGFR2* (p.Cys382Arg, c.1147T>C, corresponding to C382R in the canonical isoform). The presence of the mutation was analysed in samples from different embryonic origins by Sanger sequencing and digital droplet PCR. Saliva, blood, dark hair and bold hair did not show the mutation detected in the skin lesion (Supplementary Figure 1).

Discussion

In 2011, Petit A. et al.[1] proposed the term "RAVEN" for a group of patients with similar skin lesions, described in the literature under the term nevoid acanthosis nigricans, which followed a localized distribution along Blaschko's lines. These lesions are not usually correlated with endocrinopathy or malignancy, as is typical for acanthosis nigricans. [1]

Mutations in *FGFR3* were initially described in the pathogenesis of RAVEN. Somatic activating mutations in *FGFR3* have also been identified in seborrheic keratoses (SK) and epidermal nevi (EN). The point in fetal development when the mutation occurs, based on the migration of cells during embryogenesis, explains the topography of the lesions. Early embryonic somatic mutations (postzygotic) result in a linear configuration of EN, whereas the late somatic mutations (postembryonic) causing SK result in the concentric proliferation of the mutated cell clone, resulting in the rounded shape. Vabres[2] proposed that the specific clinical characteristics of RAVEN are due to the coalescence of rounded elements in a linear or segmental arrangement, due to a type II mosaicism caused by loss of heterozygosity. [2] More recently, the same *FGFR2* p.Ser252Trp (c.755C>G; NM_000141) mutation has been identified in affected skin tissue of three unrelated patients with RAVEN, strongly supporting the pathogenic role of these mutations.[3] Tanaka[4] et al. presented a case of congenital extensive linear keratinocytic epidermal nevi of the trunk and acral skin caused by a somatic *FGFR2*

p.Cys382Arg mutation, the same mutation identified in our patient. In addition, the same mutation has been identified in 5 cases of cerebriform sebaceous nevus on the scalp and none of these children had neurological issues.[5]

We found no other cases of RAVEN associated with autism, although it has been suggested that neuronal growth regulator 1 and *FGFR2* cooperatively regulate cortical development and core behaviors related to autism in mice.[6]

In conclusion, we present a case of RAVEN caused by a heterozygous mutation in *FGFR2.*The role of the FGFR2 mutation in autism should be further evaluated in this patient.

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FIGURE LEGENDS

Figure 1. Skin lesions at 18 months of age. A, B Multiple light brown papules and rounded and oval plaques with well-defined borders linearly distributed on the posterior aspect of the left leg. C. Rounded skin-colored papules following a linear pattern on the sole of the left foot.

Figure 2. Hair heterochromia. Lighter brown hair in the parieto-occipital region at 24 months of age.

Figure 3. Histopathology showed hyperkeratosis, orthokeratosis with acanthosis, and papillomatosis without alterations in melanocytes, the dermis, or hypodermis (H&E, 20×).

Supplementary Figure. *FGFR2* genomic analysis in samples from different embryonic origins. **A)** Next generation sequencing-IGV representation of the gain-of-function mutation in *FGFR2* identified in codon 382 corresponding to a mutant allele frequency of 7.1% of the skin lesion. **B)** The presence of the mutation was tested in skin, saliva, blood, dark hair and bold hair by Sanger Sequencing and it was not detected in any of the samples (representative chromogram). The mutation was not validated in the skin lesion most probable due to the lack of sensitivity of the technique. **C)** In order to test the mutation with higher sensitivity, a digital droplet PCR (ddPCR) assay was designed and the presence of the mutation was tested in skin, saliva, blood, dark hair and bold hair. With this accurate technique the mutation in the skin lesion could be confirmed (blue dots in left panel) with a mutant allele frequency of 6.55%. The rest of the samples tested negative for the mutation (representative plot in right panel).