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Novel postzygotic KRAS mutation in a Japanese case of epidermal nevus syndrome presenting with two distinct clinical features, keratinocytic epidermal nevi and sebaceous nevi

Satomi Igawa1, Masaru Honma, Masako Minami-Hori, Etsushi Tsuchida, Hajime Iizuka, Akemi Ishida-Yamamoto

A novel postzygotic *KRAS* mutation in a Japanese case of epidermal nevus syndrome presenting with two distinct clinical features: keratinocytic epidermal nevi and sebaceous nevi

A novel postzygotic *KRAS* mutation in ENS

Satomi Igawa[1], Masaru Honma[1], Masako Minami-Hori[1], Etsushi Tsuchida[2], Hajime Iizuka[1], and Akemi Ishida-Yamamoto

1. Department of Dermatology, Asahikawa Medical University, Asahikawa, Japan
2. Department of Pediatrics, Asahikawa Medical University, Asahikawa, Japan

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Corresponding author: Satomi Igawa, Department of Dermatology, Asahikawa Medical University, Midorigaoka-Higashi 2-1-1-1, Asahikawa 078-8510, Japan, Tel: +81 0166 68 2523, Fax: +81 0166 68 2529, E-mail: igasato@asahikawa-med.ac.jp

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Dear Editor,

Epidermal nevus syndrome (ENS) is a heterogeneous congenital disorder characterized by the presence of epidermal nevi associated with systemic involvement. Keratinocytic epidermal nevus (KEN) syndrome and sebaceous nevus (SN) syndrome are included in ENS which share the same postzygotic *HRAS* and *KRAS* gene mutations that is relevant for cell proliferation.[1,2] A *HRAS* mutation can induce nevus marginatus, a combined nevus of KEN and SN, [3] and this suggests an identical genetic background of KEN and SN. Here, we report a case of ENS exhibiting both KEN and SN characteristics caused by a novel postzygotic *KRAS* mutation.

A three-year-old Japanese girl presented with multiple nevoid lesions along Blaschko lines on the left side of her body that she had since birth. The skin lesions, which were light red at the neonatal stage (Fig. 1a), had transformed into two distinct types: yellowish plaques suggesting SN on the sebaceous gland-rich craniofacial area, and brownish verrucous lesions suggesting KEN on the trunk and extremities (Fig 1b). Histological evaluation showed papillomatosis and acanthosis with overlying laminated hyperkeratosis (Fig. 1c and d). Detailed examination revealed delayed eruption of teeth, a cerebral arachnoid cyst (Fig. 1e) and optic atrophy on her left hemicorpus. After obtaining informed consent under institutional approval and in adherence to the

principles of the Declaration of Helsinki, genomic DNA was separately extracted from the KEN-like lesional epidermis/dermis and nonlesional epidermis of the patient. Each exon of *HRAS* and *KRAS* genes was amplified by polymerase chain reaction using specific primer-pairs[1], and the direct sequencing revealed a missense mutation of *KRAS* c.34G>T (p.G12C) in lesional epidermis but not in lesional dermis, nonlesional epidermis or parental blood DNA (Fig. 1f). Immunohistochemical staining showed increased nuclear distribution of phosphorylated ERK in both the epidermis and sebaceous glands of lesional skin (Fig 1g arrow heads). These clinical and histopathological findings led to the diagnosis of ENS.

Mutations in the 12th codon result in constitutive activation of *KRAS*.[4] According to the COSMIC database, the *KRAS* c.34G>T mutation has been described as an oncogenic mutation in various carcinomas. To our knowledge, this is the first report describing a case of ENS with this mutation. As the mutation and activation of ERK, one of main mediators in downstream KRAS signaling, were specifically detected in the lesional epidermis, we assumed that *KRAS* c.34G>T resulted in increased tissue proliferation.

While there is no effective treatment for ENS at present, the molecular mechanism suggests a potency of treatment using signal inhibitors. The appearance of

skin lesions can be a major ENS related problem for cosmetic reasons. Therefore, topical application of these chemicals might be as therapeutically promising as rapamycin used for skin lesions found in tuberous sclerosis.[5]

KEN and SN syndrome have been considered as different diseases. However, clinical features and genetic analysis of our case strongly suggest communal pathogenesis. Clinical feature variations of these diseases may depend on the developmental stages at which the mutation occur and/or anatomical parts with different densities of pilosebaceous units.

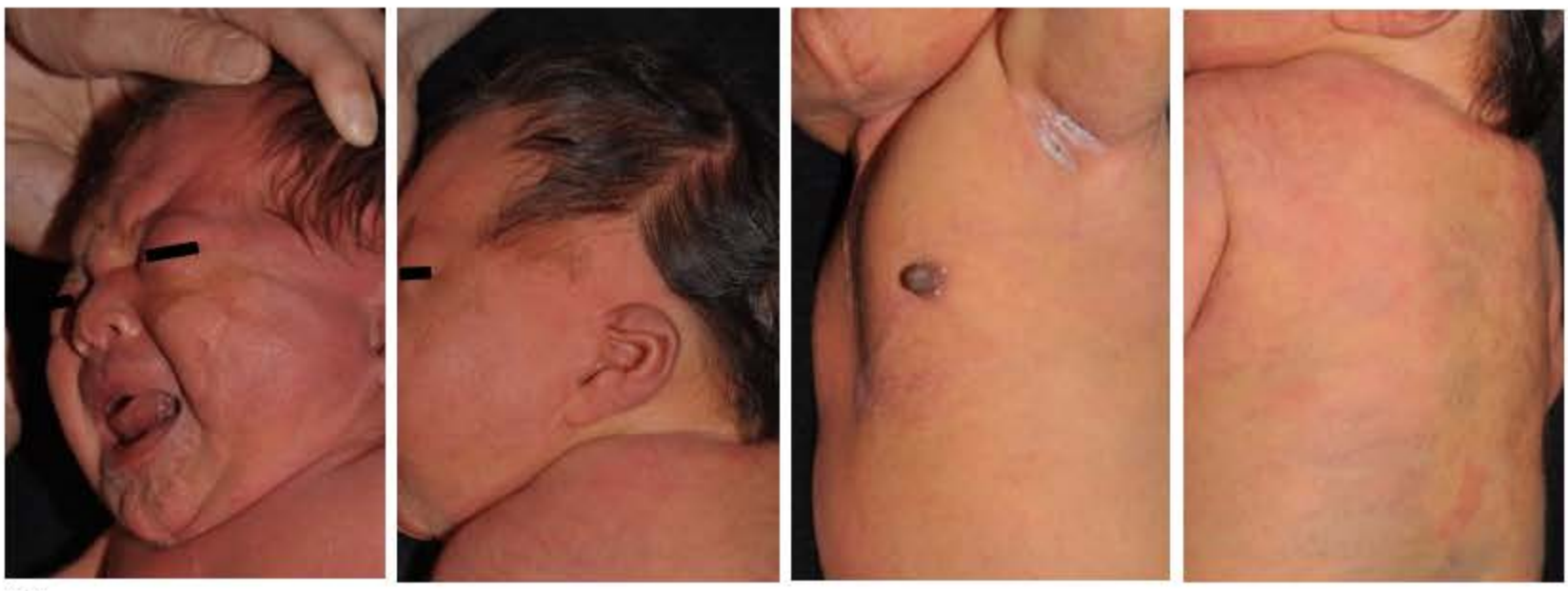
References

1. Groesser L, Herschberger E, Ruetten A, et al. Postzygotic HRAS and KRAS mutations cause nevus sebaceous and Schimmelpenning syndrome. *Nat Genet* 2012; **44**: 783-787.
2. Hafner C, Toll A, Gantner S, et al. Keratinocytic epidermal nevi are associated with mosaic RAS mutations. *J Med Genet* 2012; **49**: 249-253.
3. Groesser L, Vogt T, Happle R et al. Naevus marginatus revisited: a combined organoid and nonorganoid epidermal naevus caused by HRAS mutation. Br J Dermatol 2013; 168: 892-894.
4. Bos JL. *ras* Oncogenes in human cancer: a review. Cancer Res. 1989; **49**: 4682-4689.
5. Wataya-Kaneda M, Tanaka M, Nakamura A, Matsumoto S, Katayama I. A topical combination of rapamycin and tacrolimus for the treatment of angiofibroma due totuberous sclerosis complex (TSC): a pilot study of nine Japanese patients with TSC of different disease severity. Br J Dermatol. 2011; **165**: 912-6.

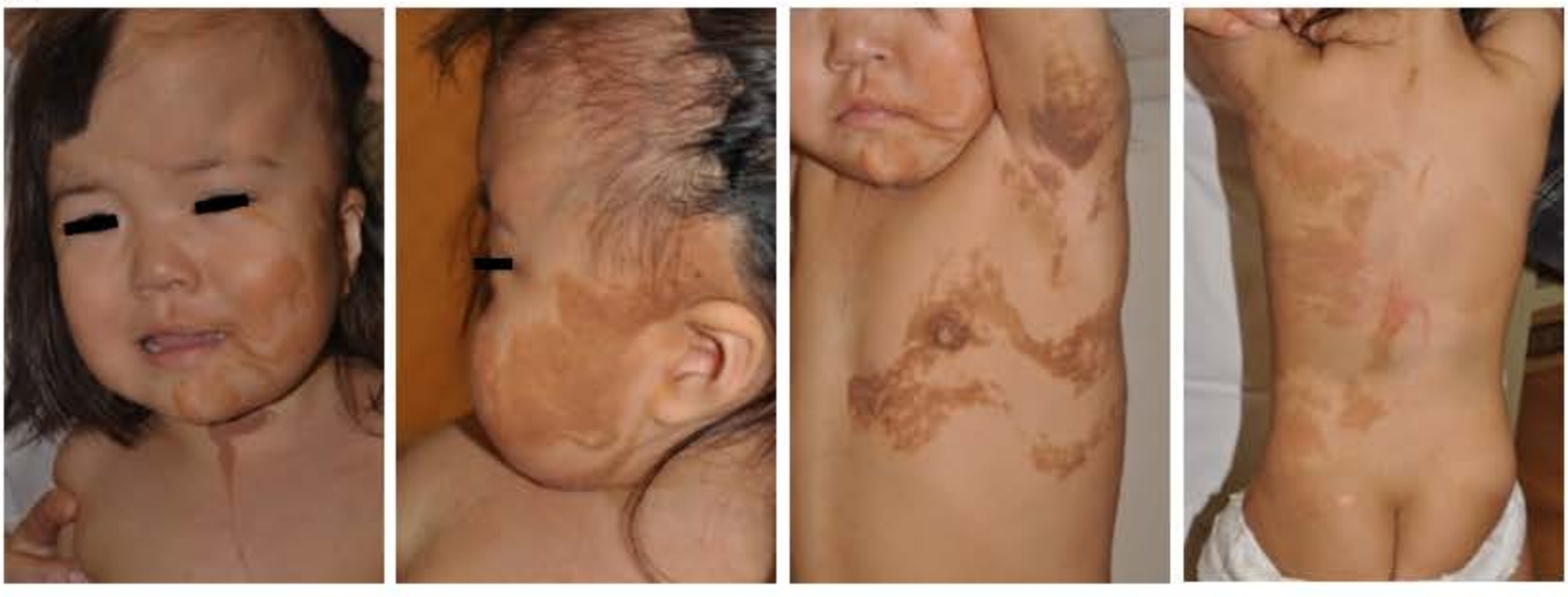
Figure legends

Figure 1. (a) Clinical manifestations at 0 years old. Light red nevi distributed on the left side of her body along Blaschko lines. (b) At present, the distribution of nevi has not changed, but the appearance has changed into two types: yellowish plaques on the head and face, and dark brownish verrucous plaques on the trunk and extremities. (c, d) Biopsy specimens were obtained from a verrucous plaque suggesting KEN (lesion) and normal skin (nonlesion) of her trunk when she was 2 years old. Hematoxylin and eosin-stained section of the lesional skin (c) exhibited papillomatosis and acanthosis with overlying laminated hyperkeratosis compared with nonlesional skin (d). Immature and abnormal pilosebaceous units were not evident (c). These features support the clinical appearance of KEN. (e) Magnetic resonance imaging of the brain (T2 weighted image) revealed a left cerebral arachnoid cyst. This is a coronal sectioned image. (f) Identification of a novel point mutation of the *KRAS* gene. The *KRAS* c.34G>T mutation is indicated by an arrow in the left panel showing lesional epidermis. We did not detect the point mutation in her lesional dermis, nonlesional epidermis or peripheral blood leukocytes (not shown). (g) Expression of pERK of both lesion epidermis (left panel) and sebaceous gland (middle panel) are increased in the nucleus as compared to that of nonlesional epidermis (right panel). Immunohistochemical staining.

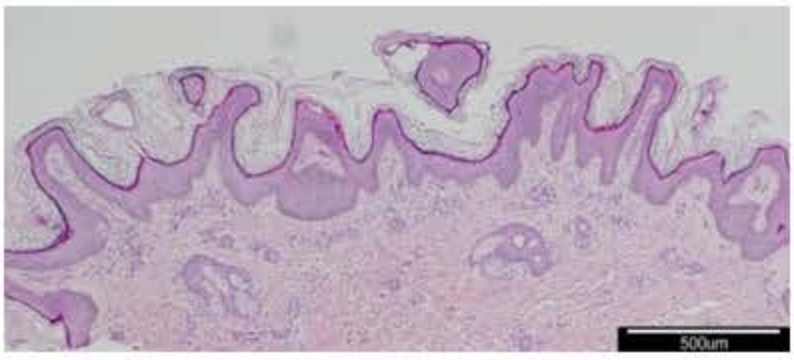
(a)



(b)



(c)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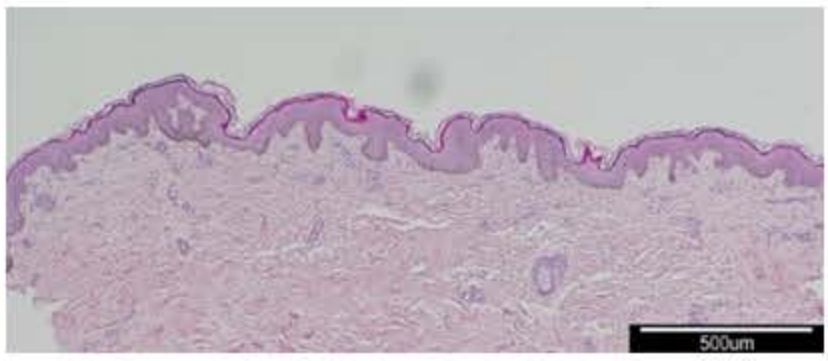
(d)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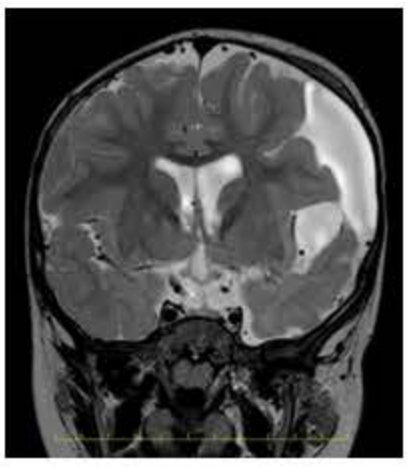
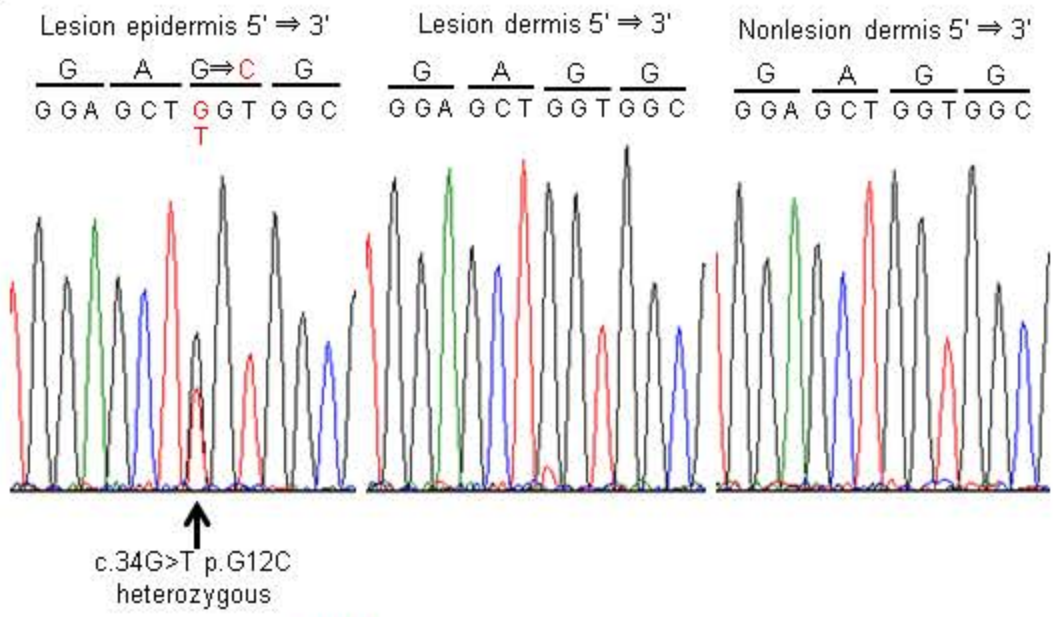
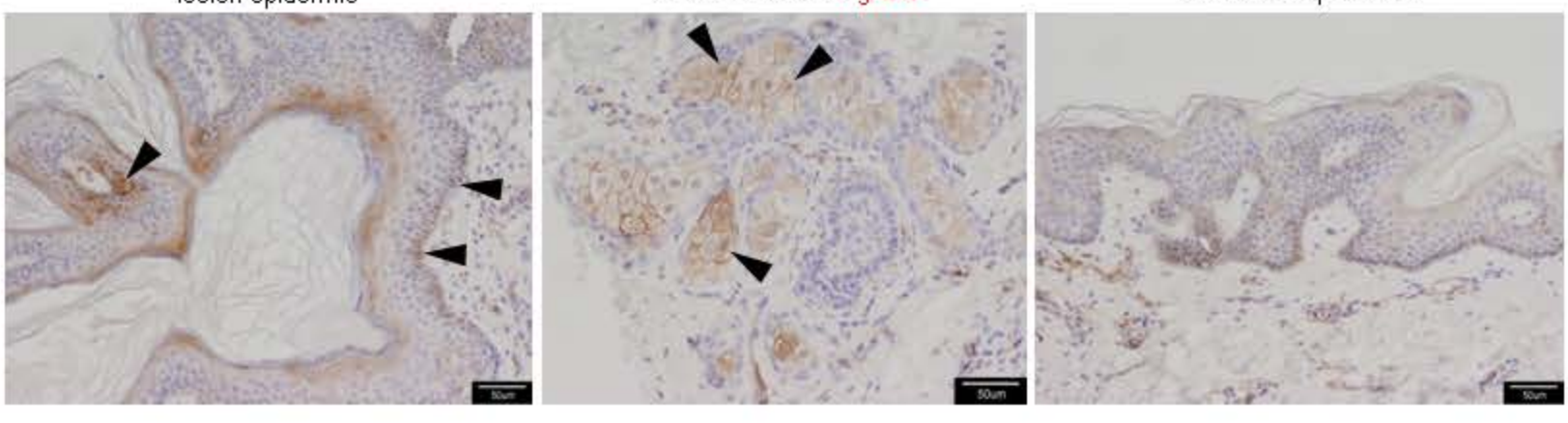
(e)



(f)


Lesion epidermis 5' ⇒ 3'
G A G⇒C G
G G A G C T G G T G G C
Lesion dermis 5' ⇒ 3'
G A G G
G G A G C T G G T G G C
Nonlesion dermis 5' ⇒ 3'
G A G G
G G A G C T G G T G G C
c.34G>T p.G12C
heterozygous

(g)


lesion epidermis
lesion sebaceous gland
nonlesion epidermis