

Phacomatosis pigmentokeratolica: post-zygotic HRAS mutation with malignant degeneration of the sebaceous naevus

Short running title:

PPK with HRAS mutation and multiple BCCs

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Phacomatosis pigmentokeratolica: post-zygotic HRAS mutation with malignant degeneration of the sebaceous naevus

Phacomatosis pigmentokeratolica is a rare epidermal naevus syndrome characterised by the coexistence of a sebaceous naevus arranged along Blaschko lines and a speckled lentiginous naevus arranged in a checkerboard pattern. Phacomatosis pigmentokeratolica is a mosaic form of a RASopathy, with recurrent heterozygous *HRAS* variants c.37G>C (p.Gly13Arg) and c.182A>G (p.Gln61Arg) most commonly found in the epidermal and melanocytic naevus¹. A novel *KRAS* c.35G>C (p.G12A) variant has also been described, highlighting the potential for concomitant visceral malignancies associated with phacomatosis pigmentokeratolica². A recent case described phacomatosis pigmentokeratolica with basal cell carcinoma (BCC), syringocystadenoma papilliferum, and trichilemmoma³. Extracutaneous features have been described, including neurologic, ophthalmic, vascular and skeletal defects.

We report a 22-year-old man with a history of phacomatosis pigmentokeratolica, with a pathogenic *HRAS* variant in the sebaceous lesion, mosaic *HRAS* variant in the lentiginous lesions, and wild-type *HRAS* sequence in blood. He was born at 38-weeks' gestation following an unremarkable pregnancy; a congenital sebaceous naevus was evident. This was treated with dermabrasion and multiple excisions. The sebaceous lesion extended to the gingiva on the left side. The lentiginous lesions arose aged 12 years. A left scalp tissue expander was inserted aged 17, but was removed due to expander breakdown and infection. The patient completed High School, but reported significant learning difficulties. He denied any history of seizures, visual symptoms, or neurological symptoms. Multiple BCCs have been excised from the sebaceous naevus over the past two years.

Examination revealed a large sebaceous naevus covering the left scalp, face and neck. Within areas of hyperpigmentation on the back, left arm and left leg, there were multiple lentiginous and

melanocytic naevi. The lesions were clearly demarcated along the midline (Figures 1 & 2). Visual and auditory examinations were normal. A computer tomography of the head and neck showed no central nervous system abnormality.

DNA extracted from punch biopsies from the sebaceous naevus in the left postauricular region showed a pathogenic heterozygous variant, NM 005343.3(HRAS):c.37G>C (p.Gly13Arg) and mosaicism of this variant in the lentiginous naevus on the left forearm. Analysis of peripheral blood showed a wild-type sequence of *HRAS*. These results were consistent with mosaicism. Genetic counselling was provided to the patient and his family.

This case supports the hypothesis that both naevi arose from a single postzygotic *HRAS* mutation in a pluripotent progenitor cell¹. Based on current evidence, the *HRAS* c.37G>C variant is classified as pathogenic. Functional studies show that the c.37G>C variant increases *HRAS* activity.⁴ Post-zygotic somatic mosaicism of an activating *RAS* mutation may compromise an ectodermal, mesodermal, and endodermal differentiation, leading to cutaneous and extracutaneous features of phacomatosis pigmentokeratocica. Generally, the epidermal and melanocytic proliferations remain as benign hamartomas, however basal cell carcinoma and melanoma have been reported in each lesion respectively. The *HRAS* c.37G>C (p.Gly13Arg) mutation has been described in malignant transformation in phacomatosis pigmentokeratocica previously.⁵ It is therefore precautionary to consider that identification of this mutation likely increases the risk of tumorigenesis in either lesion, with consequent appropriate long-term surveillance.

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Figure Legends:

Figure 1:

- a) Naevus sebaceous extending over the left face, neck, and periauricular regions. Speckled-lentiginous naevus showing a checkerboard appearance on the left neck and upper back. Extensive surgical resection and reconstruction noted.
- b) Linear arrangement of the lentiginous naevus on the right neck.

Figure 2:

- a) Naevus sebaceous affecting the left face and ear.
- b) Multiple lentiginous and melanocytic naevi on the arms and trunk, clearly demarcated along the midline. Epidermoid/sebaceous naevus is seen on the left lower chest.



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