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Multiple hereditary infundibulocystic basal cell carcinoma: report of a sporadic case with a novel pathogenic germline variant in *SUFU*

Giulia Pascolini,[1,2] Giovanna Floriddia,[3] Luca Fania,[4] Barbara Bellei,[5] Laura Eibenschutz,[6] Vito Gomes,[7] Daniele Castiglia[3]

[1]Genetic Counselling Unit, Istituto Dermopatico dell'Immacolata IRCCS, Rome; [2]Rare Skin Diseases Center, Istituto Dermopatico dell'Immacolata IRCCS, Rome; [3]Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell'Immacolata IRCCS, Rome; [4]Skin Cancer Center, Istituto Dermopatico dell'Immacolata IRCCS, Rome; [5]Laboratory of Cutaneous Physiopathology and Integrated Center of Metabolomics Research, San Gallicano Dermatological Institute IRCCS, Rome; [6]Oncologic and Preventative Dermatology Unit, San Gallicano Dermatological Institute IRCCS, Rome; [7]Pathology Anatomy Unit, Istituto Dermopatico dell'Immacolata IRCCS, Rome, Italy

Correspondence to: Giulia Pascolini, MD, PhD, Genetic Counselling Unit, Istituto Dermopatico dell'Immacolata IRCCS, Via dei Monti di Creta, 104, 00167 Rome, Italy. E-mail: g.pascolini@idi.it

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Ethics approval and consent to participate: the study was conducted according to the Declaration of Helsinki and has been approved by the Institutional Review Board of Istituto Dermopatico dell'Immacolata IRCCS (ID #578/3, 2023).

Consent for publication: informed consent for the publication of clinical data and images was obtained from the patient.

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Dear Editor,

Germline loss-of-function variants in *SUFU* (MIM*607035), a component of the Hedgehog (HH) signaling pathway, have been associated with multiple hereditary infundibulocystic basal cell carcinoma (iBCC, MIM#604451). This is a yet undefined clinicopathological entity with features that are often distinct from basal cell nevus syndrome (BCNS, MIM#109400).[1] In carriers of germline *SUFU* variants, basaloid neoplasms tend to arise at a later age compared with BCNS; the iBCC subtype is more frequently observed, and jaw cysts have not been reported.[2,3]

We report the case of a 50-year-old Italian woman who was clinically evaluated for multiple facial skin-coloured papules that gradually developed over the past 10 years and were localized at the palpebral, nasal, and perioral regions. Palmoplantar pits, jaw cysts, dysmorphisms, or other features suggestive of BCNS were not identified (Figure 1A). The family history was unremarkable. Histopathological examination of one of the nasal lesions revealed a horn cyst surrounded by anastomosing cords and strands of basaloid cells, consistent with iBCC (Figure 1B). A clinical exome sequencing (Illumina, San Diego, CA) was performed on a patient's blood sample, disclosing the heterozygous c.900_903delCTCT(p.Ser301Alafs*11) frameshift variant in *SUFU*, which was *de novo* and predicts the premature truncation of the protein (Figure 1C). The deletion has not been previously reported in the literature, and no allele frequency data are available in the gnomAD population database. The variant can be classified as likely pathogenic (class 4, pathogenic very strong [PVS1] and pathogenic moderate [PM2] criteria), according to the American College of Medical Genetics (ACMG) guidelines. Since SUFU protein functions as a tumor suppressor by inhibiting the GLI oncogenic component of the HH signaling, we also determined the zygotic status of the c.900_903delCTCT variant in the DNA extracted from microdissected, formalin-fixed paraffin-embedded sections of the patient's iBCC. Sequencing of the variant revealed a homozygous state, indicative of loss of the wild-type allele through a potential second-hit mechanism.

Clinicopathological and phenotype spectrum of patients with iBCC has not been well delineated. Thus, we propose this additional case as a further set of data. Clues to the diagnosis came from the presence of multiple facial papules that the patient noticed when she was 40, the absence of extracutaneous features, and the histopathology of an individual lesion, which presented morphological features of an iBCC subtype. The association with *SUFU* anomalies is thought to be the reason for the indolence of these lesions, which usually do not require surgical treatment. Nevertheless, some patients may develop more aggressive types of BCC, which have been associated with a high burden of UV-induced somatic pathogenic variants, as well as with sun exposure and skin type.[2] Importantly, *SUFU*-associated iBCCs do not respond to the pharmacological therapy with

Smoothened (SMO) inhibitors that target upstream elements of the HH pathway.[2,4] Moreover, a risk for life-threatening medulloblastomas or meningiomas is observed in patients with germline *SUFU* variants.[1,3] In our patient, brain magnetic resonance imaging (MRI) surveillance is currently negative for both neoplasms. She is receiving regular follow-up care, including palliative CO_2 laser treatment for skin lesions and the use of a high-protection sunscreen containing nicotinamide.

Collectively, histopathological and genetic investigations in HH syndromes are essential for planning appropriate healthcare and for the early identification of family carriers, enabling timely management.

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Figure 1. A) A view from the left side of the patient's face showing multiple skin-coloured papules, the majority of which are concentrated on the nasolabial folds and periorbital regions; **B**) iBCC with a typical horn cyst surrounded by anastomosing cords and strands of basaloid cells (original magnification x 40); **C**) Sanger sequencing chromatograms showing the c.900_903delCTCT variant at heterozygous status in the germline DNA (blood) (upper) and at the homozygous status in the somatic DNA purified from the tumor (lower), likely due to the second-hit on the trans-allele.