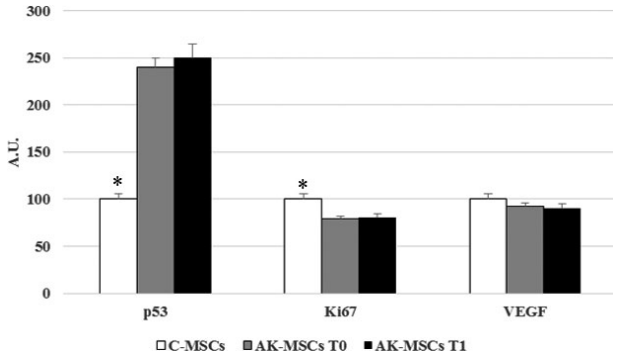

Figure 2 Densitometric analysis of p53, Ki67 and VEGF. Histogram referred to the densitometric analyses of the immunoreactive bands (quantified as ratio between band relative to p53/Ki67/VEGF and β-actin in corresponding samples, revealed by arbitrary units). Values are means ±DS from analyses performed on six actinic keratosis (AK)-patients (before and after ingenol mebutate treatment) and seven healthy controls $*P < 0.05$ C-mesenchymal stem cells (MSCs) vs AK-MSCs.

the drug can spare a significant number of stem cells is foreseeable.

Finally, literature's data on the efficacy and long-term follow-up of the IM gel treatment show that it does not always produce total clearance (only in 34.1–42.2% of patients)[8] or a clearance sustained over time (only 44.0–46.1% of patients)[9] of AKs. In addition, clinical cases of rapid progression of AK to invasive SCC after treatment with IM have been reported.[10] These data are in line, although indirectly, with results of our study and allow us to hypothesize that the IM gel does not act on AK-MSCs that may be the real responsible of the onset and development of the lesions. Future therapeutic strategies could be directed to the eradication of MSCs of AKs, considering their peculiar cytokinetic and relationship with the tissue niche. New drugs should selectively affect the AK-MSCs immunobiology, becoming able to offer greater potential for treatment with reduced local and systemic toxicity.

A. Campanati,[1] I. Bobyr,[1] G. Sorgentoni,[2] F. Diotallevi,[1] M. Caffarini,[2] P. Pellegrino,[2] R. Di Primio,[2] A. Offidani,[1,*] M. Orciani[2]

[1]Department of Clinical and Molecular Sciences - Dermatological Clinic, Università Politecnica delle Marche, Ancona, Italy, [2]Department of Molecular and Clinical Sciences - Histology, Università Politecnica delle Marche, Ancona, Italy

*Correspondence: A. Offidani. E-mail: a.offidani@ospedaliriuniti.marche.it

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Systematized naevoid hypertrichosis may herald Happle–Tinschert syndrome

Dear Editor,

Happle–Tinschert syndrome (HTS) is characterized by segmentally arranged basaloid follicular hamartomas (BFHs) associated with osseous, dental and cerebral abnormalities.[1] To date, fifteen additional cases have been described under this designation.[2–5] The disorder is caused by a postzygotic mutation in the gene smoothened (*SMO*).[5,6] In several reports, patches of hypertrichosis have been documented.[1,2] The purpose of this article is to emphasize that such naevoid hypertrichosis may sometimes be a diagnostic marker of HTS.

A 6-month-old girl who was born from healthy, non-consanguineous parents presented multiple patches of pronounced congenital naevoid hypertrichosis involving mainly the left side of her body including the cheek, nasolabial area, upper and lower eyelids, and groin (Fig. 1a–c). On her left leg, the increased hairiness showed a segmental, almost linear arrangement. In addition, she had rudimentary postaxial and preaxial polydactyly on the ipsilateral hand and foot. (Fig. 1d). On the

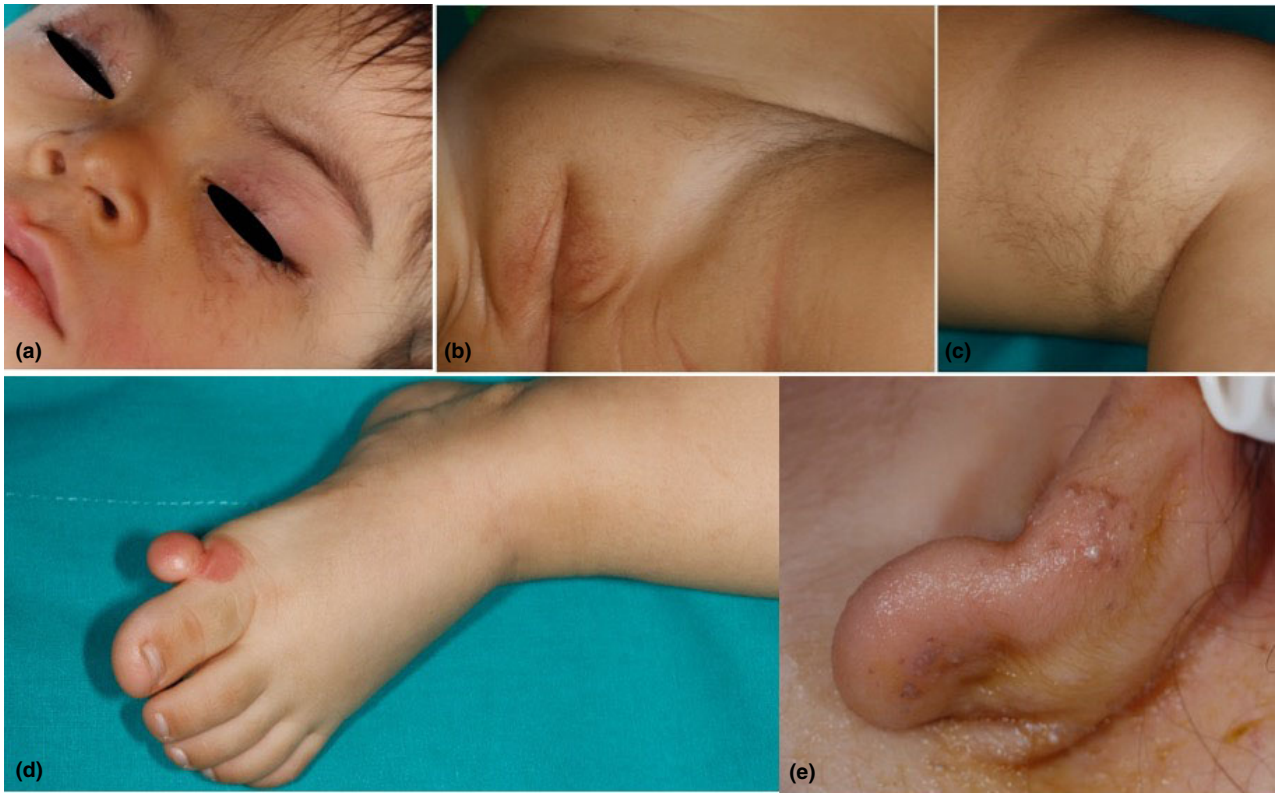

Figure 1 Bilateral palpebral hypertrichosis (a); Blaschkoid distribution of hypertrichosis on the left leg extending from the inguinal region (b) to the upper leg (c); rudimentary preaxial polydactyly of the left foot (d); Linear arrangement of papules on the left ear, with comedo-like plugs (e).

helix, some scattered hyperpigmented papules, in part with a central comedo-like plug, were arranged in a linear distribution (Fig. 1e). On the right side, small patches of hypertrichosis involved the upper eyelid and the tip of her nose, whereas a Blaschko-linear hypopigmentation with partial hypertrichosis was noted on her abdomen. Histopathological examination of biopsies obtained from the papules involving her left helix revealed strands of basaloid cells that proliferated downwards from the follicular infundibulum, forming horn cysts and numerous anastomoses with a lattice-like pattern compatible with BFHs (Fig. 2). Magnetic resonance imaging of the brain showed bifrontal cortical alterations and agenesis of the corpus callosum. A clinical diagnosis of HTS was made, and molecular analysis of *SMO* performed in a biopsy sample of BFH revealed the presence of the recurrent mutation c.1234C>T (mosaic), chr7 (GRCh37/hg19):128846398 C>T p. (Leu412Phe) in an estimated proportion of 44% of tissue cells. The mutation was found to be absent in the blood. (A previous molecular analysis had excluded a mutation in *PTCH*.)

In 2016, Happle and Tinschert suggested that HTS was a particular 'dermatological' variant of Curry–Jones syndrome.[3,7] Recent research supports the notion that these are different syndromes caused by the same gene defect.[5] In this context, it may be mentioned that Robert Gorlin himself has discriminated between 'Curry–Jones syndrome' and 'unilateral or even quadrant involvement with basal cell carcinomas' that 'likely represent postzygotic somatic mutation', under which designation he categorized, what is today called HTS, as a mosaic manifestation of Gorlin syndrome.[8]

So far, small patches of congenital hypertrichosis were taken as a minor feature of HTS.[1,2] However, a pronounced systematized involvement as noted in the present case can be a significant marker of this syndrome. Such areas of increased hairiness may be important for differential diagnosis, or exclusion, of other syndromic forms of naevoid hypertrichosis as published in the past.[9,10]

The mutation found in the present case of systematized naevoid hypertrichosis predicts a missense change in the SMO protein and is known as recurrent *SMO* mutation that has also been described in Curry–Jones syndrome[3] and represents the most common *SMO* variant observed as a somatic mutation in tumours.[5]

To the best of our knowledge, this is the first child with Latin American indigenous background reported with this syndrome,

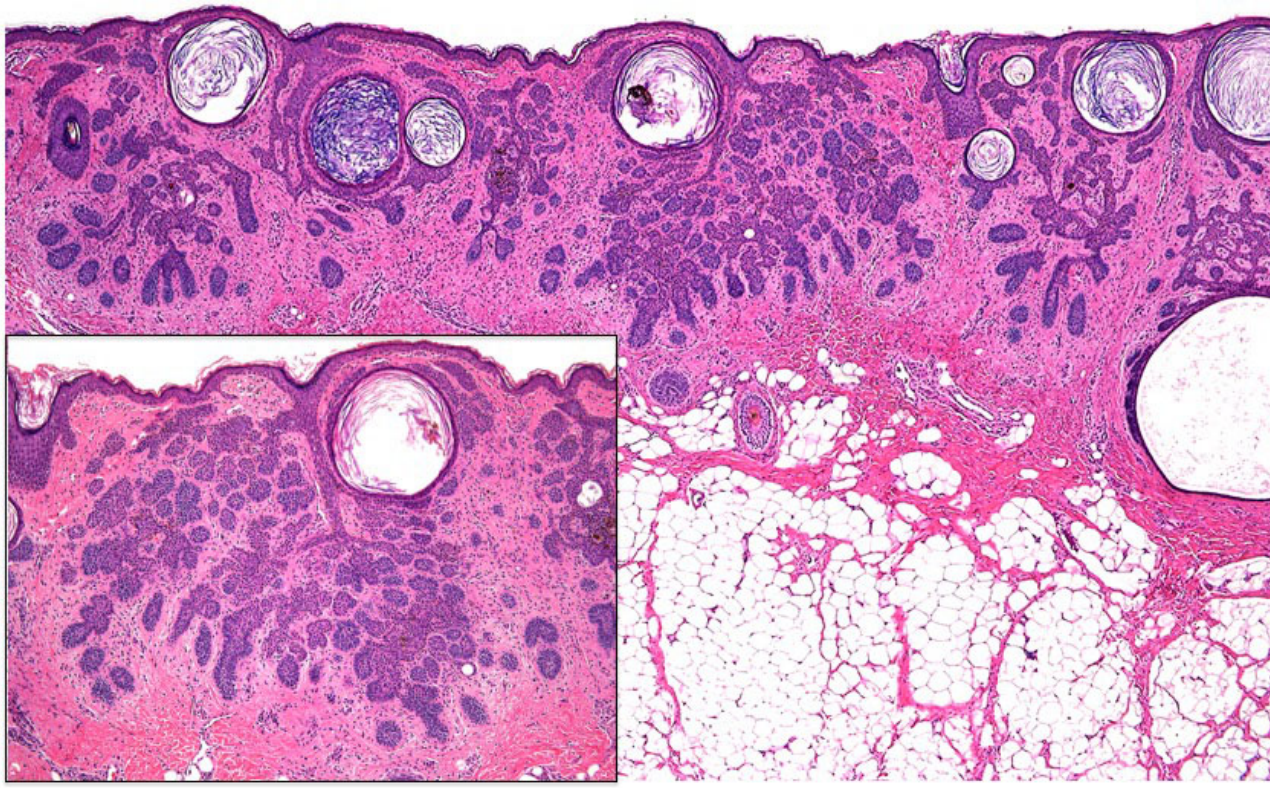

Figure 2 Strands of basaloid cells that proliferated downwards from the follicular infundibulum, forming horn cysts and numerous anastomoses with a lattice-like pattern (Inset).

emphasizing the occurrence of the same postzygotic *SMO* mutation in different populations.

T. Hasbún,[1,2] F. Reculé,[1,*] R. Happle,[3] M. Zenker,[4] D. Schanze,[4] A. Castro[5]

[1]Department of Surgery, Dermatology Service, Universidad del Desarrollo - Clínica Alemana, Santiago, Chile, [2]Dermatology Service, Hospital Exequiel González Cortés, Santiago, Chile, [3]Department of Dermatology, Medical Center – University of Freiburg, Freiburg, Germany, [4]Institute for Human Genetics, University Hospital Magdeburg, Magdeburg, Germany, [5]Department of Pathology, Universidad del Desarrollo - Clínica Alemana, Santiago, Chile

*Correspondence: F. Reculé. E-mail: f.recule.g@gmail.com

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