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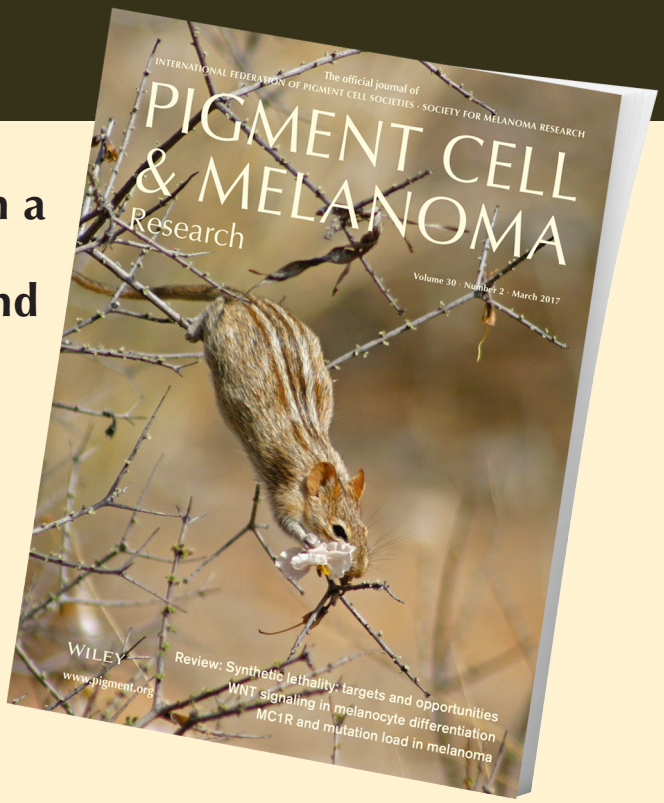

Phylloid hypomelanosis associated with a mosaic trisomy 13 in the 13q31.3-qter region: atypical phylloid distribution and typical hypomelanosis

Naoki Oiso, Kazuko Sakai, Kazuto Nishio and Akira Kawada

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Phylloid hypomelanosis associated with a mosaic trisomy 13 in the 13q31.3-qter region: atypical phylloid distribution and typical hypomelanosis

Naoki Oiso[1], Kazuko Sakai[2], Kazuto Nishio[2] and Akira Kawada[1]

1 Department of Dermatology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan **2** Department of Genome Biology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan
CORRESPONDENCE Naoki Oiso, e-mail: naoiso@med.kindai.ac.jp

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Dear Editor,

Mosaicism in human skin results in different cutaneous patterns: the narrow lines of Blaschko (type 1a), the broad lines of Blaschko (type 1b), the checkerboard pattern (type 2), the phylloid pattern (type 3), and a patchy pattern without midline separation (type 4) (Happle, 1993). The phylloid pattern is characterized by an arrangement of pigmentary disturbances reminiscent of floral ornaments or a Jugendstil painting (Happle, 1993). Phylloid hypomelanosis is characterized by congenital hypopigmented macules following the phylloid pattern. It is associated with a mosaic deletion or duplication of chromosome 13 including the 13q21-qter region (Faletra et al., 2012; Myers et al., 2015). However, the chromosomal region implicated in phylloid hypomelanosis has not so far been defined more precisely.

In this report, we describe a case of phylloid hypomelanosis with atypical phylloid distribution and typical hypomelanosis associated with a mosaic trisomy 13 in the 13q31.3-qter region. The patient was a nine-year-old Japanese girl born to non-consanguineous parents. She was referred to us with asymptomatic hypopigmented lesions on the left forearm and foreleg. The parents had no history of pigmentary disorders. She had mild sensorineural hearing loss and mild mental retardation. Physical examination revealed hypopigmented lesions along the atypical phylloid distribution on the left forearm and foreleg (Figure 1A, B), but not along the lines of Blaschko. Atypical phylloid distribution resembled lance-like or Japanese yam-like appearance.

A biopsy was taken from the hypopigmented lesion on the left foreleg. Noticeable structural abnormalities were not detected in the hypopigmented lesion (Figure 1C). Fontana-Masson staining indicated reduced production of melanin granules. Electron microscopic analysis identified the focal multitude of dysfunctional melanocytes (arrows) (Figure 1D). A higher resolution showed vacuolated mitochondria, and tiny, immature melanosomes (Figure 1E, F).

The parents provided written informed consent allowing the patient to participate in the study according to a protocol approved by the Genetic Ethics Committee of Kindai University Faculty of Medicine. The protocol was conducted according to the Declaration of Helsinki Principles. Cytogenetic analysis of 30 peripheral blood cells showed an abnormal mosaic karyotype (47, XX, +mar [origin-unknown chromosome] [6]/46, XX [24]).

Genomic DNA isolated from the peripheral blood cells was analyzed with an OncoScan FFPE Assay (Affymetrix Japan, Tokyo, Japan). The DNA (80 ng) was subjected to annealing with molecular inversion probes (MIPs) for 16 to 18 h followed by enzyme digestion and the gap-fill reaction. The circular MIPs were then linearized with a cleavage enzyme and amplified by polymerase chain reaction (PCR). The PCR products were subjected to enzymatic cleavage and fragmentation followed by hybridization for 16 to 18 h with the OncoScan array. The array was then stained and washed with the use of a GeneChip Fluidics Station 450 and loaded into a GeneChip Scanner 3000 7G (Affymetrix Japan). Array fluorescence intensity (CEL) files were generated with Affymetrix GeneChip Command Console (AGCC) software version 4.0, and the CEL files were converted to OSCHP files with OncoScan Console software 1.3. Data analysis was performed using Nexus Express software for OncoScan (Biodiscovery, El Segundo, CA, USA). The OSCHP files were processed using Nexus TuScan algorithms. Microarray analysis showed a mosaic trisomy 13 in the 13q31.3-qter (chr13:chr13:93,079,655-115,169,878) region (Figure 2).

A diagnosis of phylloid hypomelanosis was made. The differential diagnoses included systemic nevus depigmentosus and hypomelanosis of Ito. However, presentation of systemic nevus depigmentosus and hypomelanosis of Ito is seen along the lines of Blaschko.

The first notable manifestation is identification of the mosaic trisomy 13 in the 13q31.3-qter region. Phylloid hypomelanosis is linked to the presence of a mosaic deletion or duplication of chromosome 13 (Faletra et al., 2012; Myers et al., 2015). Faletra et al. (2012) performed a microarray analysis with genomic DNA from skin

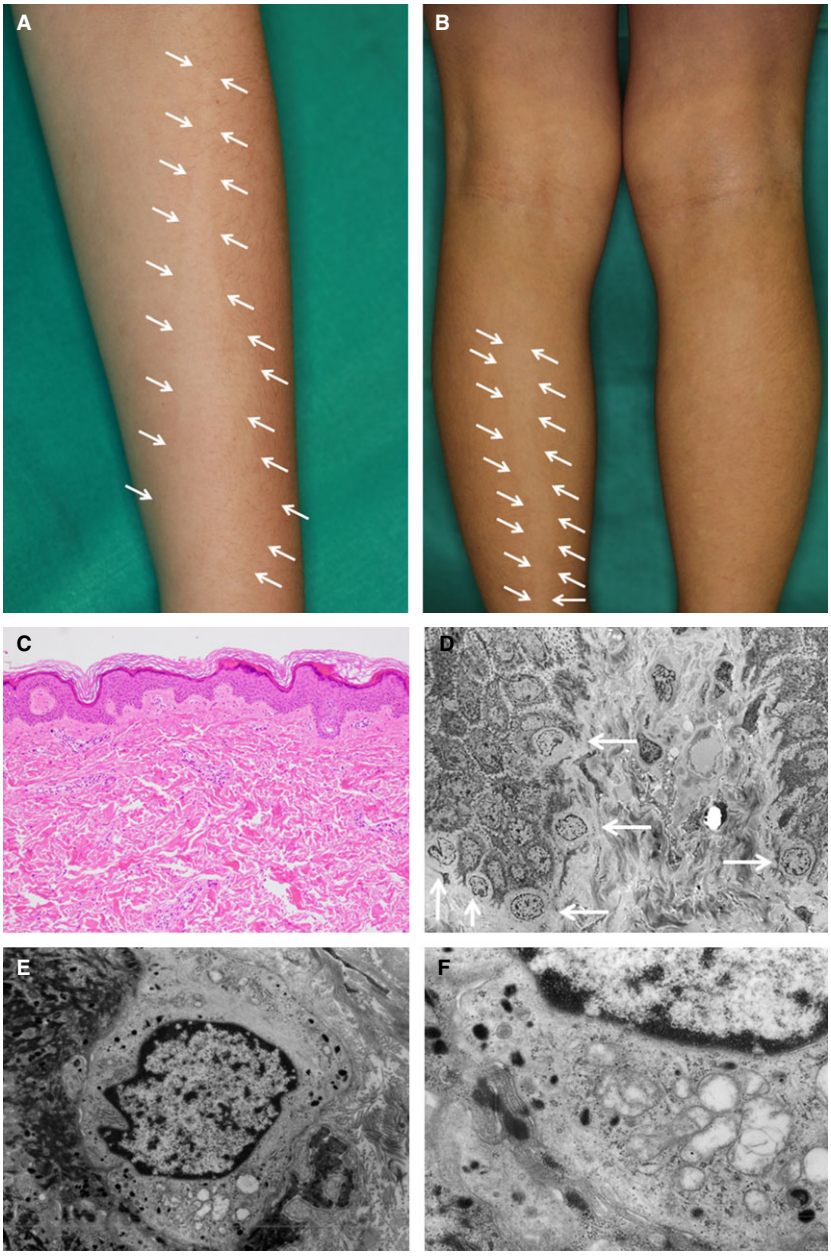

Figure 1. Clinical pictures of hypopigmented lesions along the atypical phylloid distribution on (A) the left forearm and (B) foreleg. Noticeable structural abnormalities were not detected in the hypopigmented lesion (hematoxylin and eosin stain, original magnification (C) ×100). Electron microscopic analysis identified (D) the focal multitude of dysfunctional melanocytes (arrows). (E, F) A higher resolution showed vacuolated mitochondria, and tiny, immature melanosomes ((D) ×5,000, (E) ×5,000, and (F) ×15,000).

fibroblasts of two patients with phylloid hypomelanosis and detected duplication in the 13q21.33-qter (chr13:71,024,411-115,103,529) region and deletion in the 13q13.3-qter (chr13:38,368,012-115,103,529) region. Their analysis indicates that the candidate genes are present in the 13q21.33-qter region. Faletra et al. (2012) proposed three candidates, endothelin receptor type B (*EDNRB*) in 13q22.3, ephrin-B2 (*EFNB2*) in 13q33.3, and dopachrome tautomerase (*DCT*) in 13q32.1.

Mutations in *EDNRB* cause Waardenburg syndrome, a rare neurocristopathy resulting from an abnormal migration or differentiation of neural crest cells during embryonic development (Baynash et al., 1994; Doubaj et al., 2005). Pigmentary anomalies like white forelock and white skin patches represent aberrant melanoblast migration. The ephrin-B2 signaling is suggested to be responsible for anomalous melanoblast migration (Faletra et al., 2012; Santiago and Erickson, 2002). However, *EFNB2* knockout mice have no neural crest migration problem.

Atypical phylloid distribution in our case is associated with a mosaic trisomy 13 in the 13q31.3-qter region, whereas typical phylloid distribution in previous cases is related to a mosaic of chromosome 13 in the 13q21.33-qter region. These suggest that occurrence of typical phylloid distribution is associated with a mosaic of chromosome 13 in the 13q21.33-qter region including both *EDNRB* and at least another hypothetical melanoblast migration-associated factor. We need to explore at

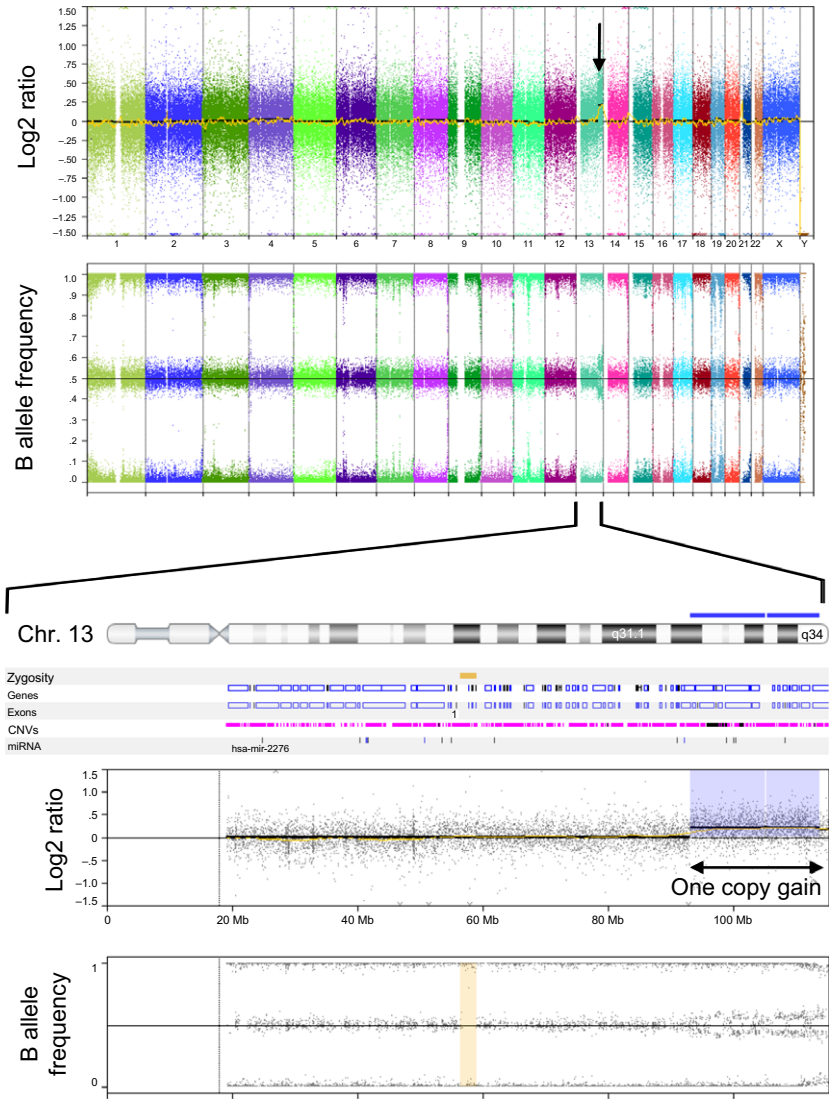

Figure 2. Microarray analysis with genomic DNA from the peripheral blood cells showed a mosaic trisomy 13 in the 13q31.3-qter (chr13:93,079,655-115,169,878) region.

least one supposed factor in the 13q31.3-qter region to induce atypical phylloid distribution.

The second notable manifestation was revealed by electron microscopic analysis. The focal multitude of dysfunctional melanocytes indicates a trace of aberrant melanoblast migration. Vacuolated mitochondria and immature melanosomes in the melanocytes signify dysfunctional melanogenesis. Nevoid pigment anomalies of pigmentary mosaicism are caused by chromosomal abnormalities disrupting the expression or function of pigmentation-associated genes (Taibjee et al., 2004). The multiplicity of pathogenesis is based on over 800 phenotypic alleles identified in mouse models of pigment disorders (Bennett and Lamoreux, 2003). In previous cases, hypomelanosis is associated with complex interactions between genes rather than simply a dose effect, because hypomelanosis exists in both mosaic deletion and duplication of chromosome 13 in the 13q21.33-qter region (Faletra et al., 2012). In this case, the mosaic trisomy 13 in the 13q31.3-qter region still preserves ability to induce typical hypomelanosis.

DCT, also known as tyrosinase-related protein-2, is involved in melanogenesis (Costin et al., 2005). We surmise that at least another unrevealed melanogenesis-associated gene exists in the 13q31.3-qter region, because tyrosinase-related protein-2 is associated with eumelanin/pheomelanin synthesis, but it is not associated with intracellular trafficking and structure of mitochondria and melanosomes (Costin et al., 2005). Lysosomal-associated membrane protein 1 (LAMP1) encoded by *LAMP1* in 13q34 is one of the candidates, because LAMP1 is supposed to regulate the positioning of lysosomes and mitochondria (Rajapakshe et al., 2015). LAMP1 is a component of melanosomes, one of the lysosome-related organelles (Boissy et al., 2005). The presence of physical and functional connection between mitochondria and melanosomes is essential for organelle biogenesis (Daniele et al., 2014). We hypothesize that

unregulated expression of LAMP1 is associated with impaired organelle biogenesis inducing vacuolated mitochondria, and tiny, immature melanosomes.

In summary, we report a case of phylloid hypomelanosis associated with a mosaic trisomy 13 in the 13q31.3-qter region. Our case may indicate that the mosaic trisomy 13 in the 13q31.3-qter region induces atypical phylloid distribution; however, the mosaic trisomy 13 in the 13q31.3-qter region may be enough to produce typical hypomelanosis. Further investigation with a case series would elucidate the multiplicity of pathogenesis in phylloid hypomelanosis.

Acknowledgements

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