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CASE REPORT

Dyschromatosis universalis hereditaria: a familial case with ultrastructural skin investigation

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ABSTRACT

Dyschromatosis universalis hereditaria (DUH) is a rare disease that is inherited both in autosomal dominant and autosomal recessive patterns. It is characterized by appearance of pinpoint to pea-sized hypo- and hyper-pigmented macules distributed in a reticulated pattern over the trunk and limbs within the first few years of life. Although the pathogenesis is still not clear, some authors proposed that decreased melanosome synthesis rate may underlie this disorder. We describe a 56-year-old female and her 24-year-old son with generalized symmetrically distributed hypo- and hyper-pigmented macules. After clinical, histological and ultrastructural examination, we proposed defect in melanosome transfer from melanocytes to keratinocytes may underlie the pathogenesis of DUH.

Introduction

The dyschromatoses are a group of rare genodermatoses characterized by the presence of asymptomatic hyper-pigmented macules admixed with variably sized hypo-pigmented macules. There are two classic forms of dyschromatoses: dyschromatosis universalis hereditaria (DUH) and dyschromatosis symmetrica hereditaria (DSH, which is also known as acropigmentation symmetrica of Dohi). In recent years, with the development of genetic analysis, ADAR1 or DSRAD gene mutations have been found in DSH but not in DUH, and therefore these two diseases are now regarded as two different entities.[1] Although the first reported case[2] and most subsequently reported cases of DUH were of Japanese origin, sporadic cases have been reported from all over the world.[3–5] Herein, we report a Taiwanese mother and her son with DUH.

Case presentation

Patient 1 was a 56-year-old Taiwanese woman who presented with generalized symmetrically distributed hypo- and hyper-pigmented macules. The skin lesions appeared in infancy and progressed with time. Patient 2 was her 24-year-old son with a history of similar skin lesions which appeared before one year of age. Physical examinations of the skin of both patients revealed disseminated hyper- and hypo-pigmented macules of varying size ranging from 2 mm to 30 mm involving almost the entire body in a symmetrical pattern, which were more prominent on the extremities with relative sparing of the palms, soles and face (Figure 1). The individual skin lesion was mottled in appearance. Hair, nails, teeth and the oral mucosae appeared normal. Both patients had normal mental and developmental milestones. They reported no extensive sun exposure, history of photosensitivity, or systemic illness prior to the onset of the lesions. The mother was married to a non-consanguineous male with no similar skin lesions. None of the mother's siblings or her parents had similar skin lesions. The family pedigree is shown in Figure 2.

We performed skin biopsies on the hypo- and hyper-pigmented lesions of both patients. The specimens were sent for hematoxylin and eosin (H&E) stain and transmission electron microscopy (TEM) study. The H&E stained specimens taken from the hyper-pigmented lesions of both patients revealed increased melanin deposition in the basal layers of the epidermis (Figure 3A). No conspicuous melanin incontinence was found. There was no acanthosis or hyperkeratosis of the epidermis and the dermis was unremarkable. The hypo-pigmented lesions were also biopsied which showed decreased melanin deposition in the basal layers of the epidermis in both patients (Figure 3B). Melanocytes were present in the basal layers of both hyperpigmented and hypopigmented areas.

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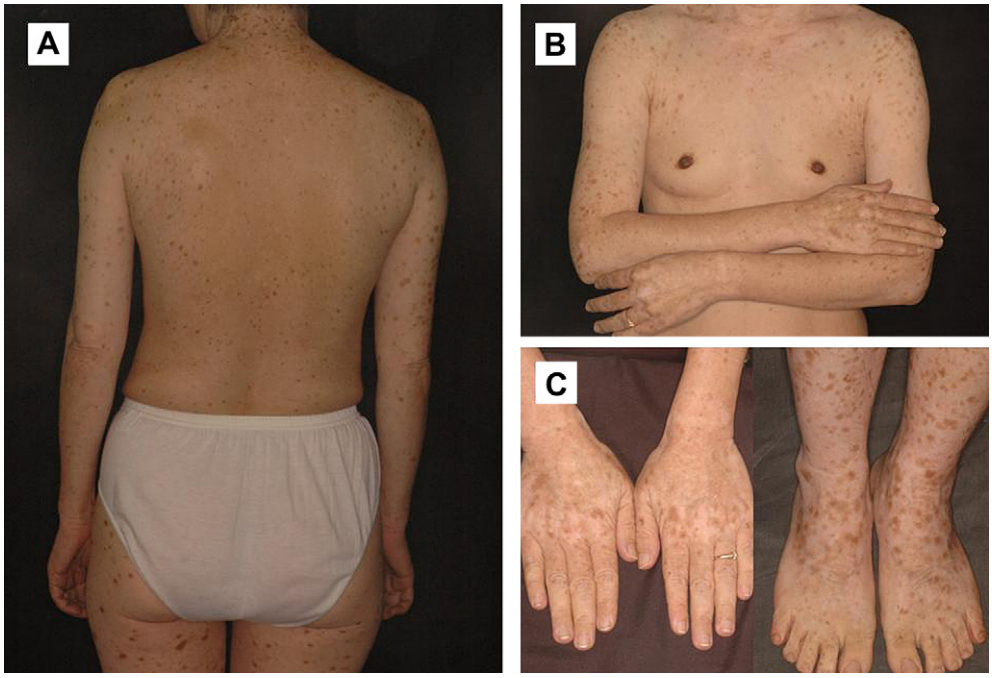

Figure 1 Clinical pictures of patient 1, generalized symmetrically distributed hypo- and hyper-pigmented macules on (A) back and (B) chest (C) distal extremities.

Ultrastructual examination via TEM revealed that the melanocyte number was similar in both the hyper- and hypo-pigmented lesions (approximately 10–15 basal keratinocytes: one melanocyte) (Figure 4A and 4B). The melanosome numbers were similar in the melanocytes of both hypo- and hyper-pigmented lesions, and melanosomes of all stages were found in the melanocytes of both lesions (Figure 4D–G). However, there were very few melanosomes noted in the adjacent keratinocytes of the hypo-pigmented lesion. In contrast, the keratinocytes of the hyper-pigmented lesions contained numerous fully melanized melanosomes which were aggregated to form melanosome complexes (Figure 4C). Most of the melanosomes were smaller than 0.5 μm.

Discussion

In this report, we described two cases of DUH and their ultrastructural skin findings. In our patients, we found there was no obvious difference in melanocyte numbers between the hyper- and hypo-pigmented lesions and the melanosome numbers in the melanocytes of both lesions were also similar. However, decreased melanosome numbers in the adjacent keratinocytes of the hypo-pigmented lesions were noted. In contrast, numerous fully melanized melanosomes were aggregated to form melanosome complexes in the keratinocytes of the hyper-pigmented lesions. According to the above findings, we proposed defect in melanosome transfer from melanocytes to keratinocytes may underlie the pathogenesis of DUH.

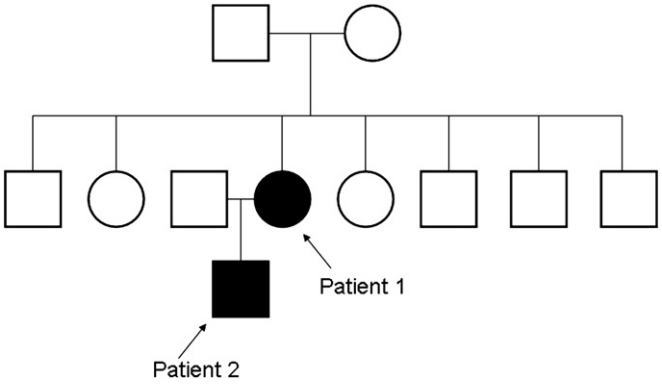

Figure 2 Pedigree of the Taiwanese family of dyschromatosis universalis hereditaria.

Autosomal dominant inheritance pattern was seen in our patients. Most of the previously reported DUH cases were also inherited in autosomal dominant pattern though some were autosomal recessive[6,7] and sporadic cases were noted.

The clinical diagnosis of DUH in these two cases was made based on the distribution of the skin lesions and the history of the patients. Other pigmentary disorders which should be considered in the differential diagnosis were reviewed and compared in Table 1.[5,8–10]

The typical DUH skin lesions were characterized by the appearance of pinpoint to pea-sized hypo- and hyper-pigmented macules distributed in a reticulated pattern over the trunk and limbs which often appeared within the first few years of life. Though mucosa and palmoplantar areas were frequently spared, some cases had oral mucosa and tongue involvement with mottled pigmentation.[11] Abnormalities of hair and nails have also been described. Associated abnormalities were rarely seen though cases with tuberous sclerosis,[12] photosensitivity and neurosensory hearing defect,[13] small stature and high-tone deafness,[14] and X-linked ocular albinism[15] had been reported. Compared to previously reported cases, the skin lesions of our patients are more prominent at extremities and less skin lesions are found on the trunk region. There are no associated abnormalities noted.

The histopathology of DUH specimens usually show normal epidermis with no acanthosis or parakeratosis. The hyper-pigmented lesions reveal an increase in melanin content of the basal layer and melanin incontinence is sometimes seen. The hypo-

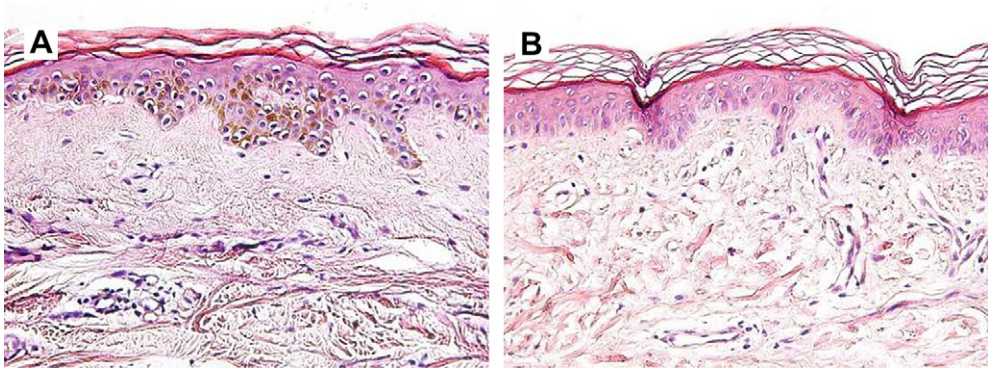

Figure 3 Skin biopsy specimen taken form patient 1. (A) Hyper-pigmented lesion showed increased melanin deposition in the basal layer of the epidermis, no conspicuous melanin incontinence was seen (H&E, 100×). (B) Decreased melanin deposition at the basal layer of the hypo-pigmented lesion (H&E, 100×).

pigmented lesions show relatively decreased melanin deposition at the basal layer.[16] In contrast to some reports, there was no conspicuous melanin incontinence in the hyper-pigmented lesion in our cases.

The etiology and pathogenesis of DUH is not clearly established. Cutaneous pigmentation depends on the number of melanocyte, the melanogenic activity within the melanocytes, the proportion of mature melanosomes and/or their transfer and distribution within the keratinocytes.[17] Yang and Wong[15] reported a DUH case with "giant pigment granules" in keratinocytes, melanocytes and dermal phagocytes among the hyperpigmented lesion, but those findings were not seen in our cases. Our findings also differed from Kim et al,[18] who found no melanosomes in the melanocytes and keratinocytes of the hypo-pigmented lesions. Our finding is consistent with Nuber et al,[8] who also found similar melanocyte numbers in both hypo- and hyper-pigmented lesions. Besides, the melanosome numbers in the melanocytes were also similar in both hypo- and hyper-pigmented lesions. In addition, Nuber et al reported positive DOPA reaction is similar (which indicates tyrosinase activity) under TEM in melanocytes of both hyper- and hypo-pigmented skin lesions. According to our findings and the finding of Nuber et al, we propose the difference in transfer and distribution of melanosomes within the epidermal melanin units may underlie the pathogenesis of DUH.

The distinct clinical and morphologic patterns between the juxtaposed hypo- and hyperpigmented macules suggest the possibility of different genotypes in the same individual which indicates cutaneous mosaicism. But the typical distribution of DUH skin lesions does not fit the patterns of clinical involvement of cutaneous mosaicism, such as lines of Blaschko, a checkerboard pattern, a phylloid pattern, a patchy pattern without midline separation, or a lateralization pattern.[19]

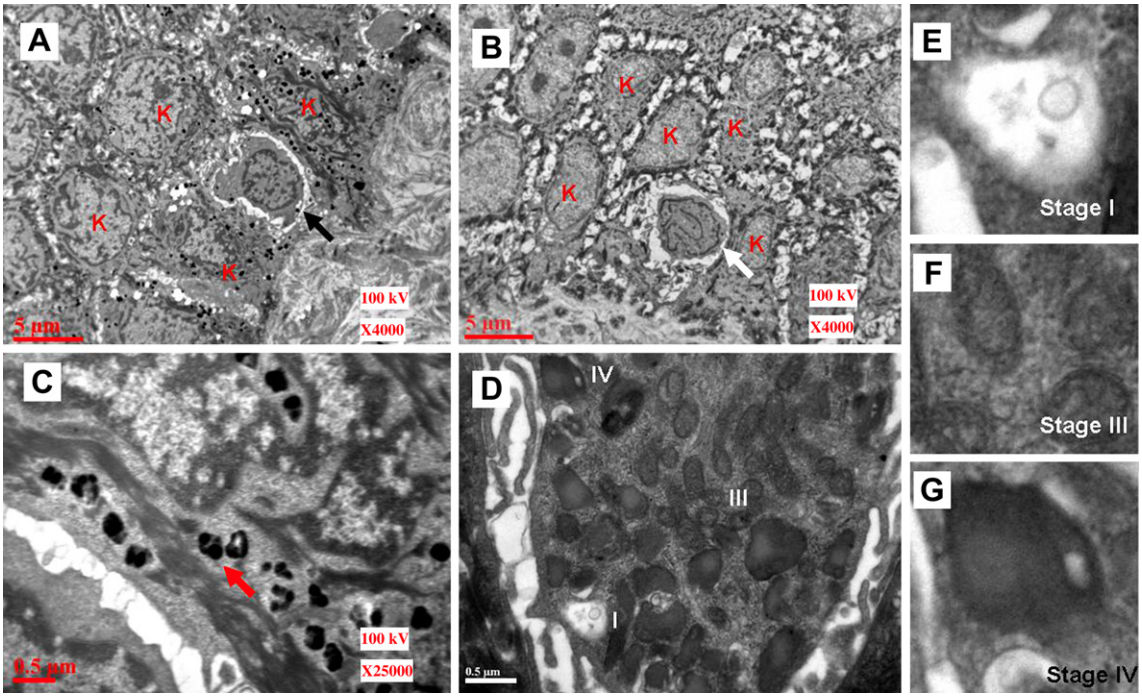

Figure 4 (A) Electron micrograph showed melanosomes in the melanocyte (black arrow) and keratinocytes of the hyper-pigmented lesion (TEM, 4000×). (B) melanocyte (white arrow) of the hypopigmented lesion, only few melanosomes are found in the adjacent keratinocytes (TEM, 4000×). (C) The melanosomes in the keratinocytes of the hyper-pigmented lesion aggregate to form melanosome complex (red arrow) (TEM, 25000×). (D) Different stages of melanosomes are found in the melanocyte of the hypo-pigmented lesion (TEM, 30000×). (E)~(G) Close view of different staged melanosomes. (K: keratinocyte; I: stage I melanosome; III: stage III melanosome; IV: stage IV melanosome).

Table 1 Differential Diagnosis of Dyschromatosis Universalis Hereditaria.[5,8–10]

	Inheritance	Genetics	Onset	Distribution of lesions	Skin Morphology	Pathology	Additional cutaneous and clinical features
Dyschromatosis universalis hereditaria	AD, Occasionally AR	6q24.2–q25.2 or 12q21–q23	Early childhood	Trunk, limbs, face, over almost all the body	Mottled hyperpigmented and hypopigmented macules	Pigmentary incontinence with increase or decrease in melanin content of the keratinocytes in basal layer, normal melanocyte number	Associated abnormalities were rarely seen though cases with tuberous sclerosis, photosensitivity and neurosensory hearing defect, small stature and high-tone deafness, X-linked ocular albinism have been reported.
Dyschromatosis symmetrica hereditaria	AD, Occasionally AR	DSRAD gene, ADAR1 gene	Early childhood	Back of hands and feet, face	Mottled hyperpigmented and hypopigmented macules	Pigmentary incontinence with increase or decrease in melanin content of the keratinocytes in basal layer, normal melanocyte number	None
Dyskeratosis congenita	X-linked, occasionally AD	X-linked: DKC1 AD: TERC	Early childhood	Neck, upper chest, upper arms	Reticulated hyperpigmented and hypopigmented macules	Melanophages in upper dermis	Mucosal leukoplakia; nail dystrophy; dental changes; hair abnormalities; ocular changes; hyposthenic body builds; dysphagia; bone marrow dysfunction; tumor predisposition
Xeroderma pigmentosum	AR	Various genes	Early childhood	Sun-exposed areas	Lentigines and hyperpigmented macules	Hyperkeratosis, chronic inflammatory infiltrate in upper dermis, irregular accumulation of melanin in basal layer, melanocyte number can be increased	Xerosis; atrophy; telangiectasia; skin tumors
Generalized Dowling–Degos disease	AD	Not identified	Young adulthood	Generalized, flexural areas, trunk, limbs	Mottled hyperpigmented and hypopigmented macules, papules	Mild hyperkeratosis, thinned epidermis, downward proliferation of rete ridges, basal hyperpigmentation	Facial pits, comedo-like papules, palmar pits, broken epidermal ridges, café -au-lait spots
Incontinentia pigmenti (Bloch-Sulzberger)	X-linked dominant	X-linked: :NEMO	At birth	Along Blaschko lines	Hyper-pigmentation in stage 3, hypo-pigmentation in stage 4	Hyper-pigmentation due to pigmentary incontinence in dermal melanocytes	Alopecia; nail dystrophy; hypo/adontia; eye abnormalities; CNS involvement
Naegeli–Franceschetti–Jadassohn syndrome	AD	17q21	Early childhood	Neck, chest, and abdomen	Brown or gray-brown reticular pigmentation	Variable pigmentation of basal keratinocytes; pronounced pigmentary incontinence	Dental anomalies; palmar/plantar hyperkeratosis; hypohidrosis; nail dystrophy
Chronic arsenic toxicity	Not inherited		Depends on the accumulation of arsenic in target tissues and its metabolism and elimination	Trunk, areola, flexural creases, any part of the body may be affected	Guttate hypopigmentation superimposed on hyperpigmentation 'raindrops on a dusty road'	Increased melanin in epidermis, no melanocystic proliferation	Increased risk of internal malignancies
Chronic radiodermatitis	Not inherited		Months to years after radiotherapy	Irradiated area	Telangiectasia and atrophy, skin cancer	Epidermal atrophy and telangiectasia, dermal melanophages and solar elastosis	None

AD = autosomal dominant; AR = autosomal recessive.

In summary, we report these two cases of DUH and their ultrastructural skin findings. Our results indicated that defects in melanosome transfer to keratinocytes may underlie this disorder. Further functional studies are needed to clarify the pathoetiology.

References

1. Suzuki N, Suzuki T, Inagaki K, et al. Mutation analysis of the ADAR1 gene in dyschromatosis symmetrica hereditaria and genetic differentiation from both dyschromatosis universalis hereditaria and acropigmentatio reticularis. *J Invest Dermatol* 2005;**124**:1186–92.
2. Urabe K, Hori Y. Dyschromatosis. *Semin Cutan Med Surg* 1997;**16**:81–5.
3. Kenani N, Ghariani N, Denguezli M, et al. Dyschromatosis universalis hereditaria: two cases. *Dermatol Online J* 2008;**14**:16.
4. Yusuf SM, Mijinyawa MS, Maiyaki MB, et al. Dyschromatosis universalis hereditaria in a young Nigerian female. *Int J Dermatol* 2009;**48**:749–50.
5. Wu CY, Huang WH. Two Taiwanese siblings with dyschromatosis universalis hereditaria. *Clin Exp Dermatol* 2009;**34**:e666–9.
6. Bukhari IA, El-Harith EA, Stuhrmann M. Dyschromatosis universalis hereditaria as an autosomal recessive disease in five members of one family. *J Eur Acad Dermatol Venereol* 2006;**20**:628–9.
7. Stuhrmann M, Hennies HC, Bukhari IA, et al. Dyschromatosis universalis hereditaria: evidence for autosomal recessive inheritance and identification of a new locus on chromosome 12q21–q23. *Clin Genet* 2008;**73**:566–72.
8. Nuber UA, Tinschert S, Mundlos S, et al. Dyschromatosis universalis hereditaria: familial case and ultrastructural skin investigation. *Am J Med Genet A* 2004;**125A**:261–6.
9. Wu YH, Lin YH. Generalized Dowling–Degos disease. *J Am Acad Dermatol* 2007;**57**:327–34.
10. Al Hawsawi K, Al Aboud K, Ramesh V, et al. Dyschromatosis universalis hereditaria: report of a case and review of the literature. *Pediatr Dermatol* 2002;**19**:523–6.
11. Sethuraman G, Srinivas CR, D'Souza M, et al. Dyschromatosis universalis hereditaria. *Clin Exp Dermatol* 2002;**27**:477–9.
12. Binitha MP, Thomas D, Asha LK. Tuberous sclerosis complex associated with dyschromatosis universalis hereditaria. *Indian J Dermatol Venereol Leprol* 2006;**72**:300–2.
13. Shono S, Toda K. Universal dyschromatosis associated with photosensitivity and neurosensory hearing defect. *Arch Dermatol* 1990;**126**:1659–60.
14. Rycroft RJ, Calnan CD, Wells RS. Universal dyschromatosis, small stature, and high-tone deafness. *Clin Exp Dermatol* 1977;**2**:45–8.
15. Yang JH, Wong CK. Dyschromatosis universalis with X-linked ocular albinism. *Clin Exp Dermatol* 1991;**16**:436–40.
16. Wang G, Li CY, Gao TW, et al. Dyschromatosis universalis hereditaria: two cases in a Chinese family. *Clin Exp Dermatol* 2005;**30**:494–6.
17. Klaus W, Lowella AG, Stephen IK, et al. *Fitzpatrick's dermatology in general medicine*. 7th ed. the United States of America: The McGraw-Hill Companies Inc.; 2008. p. 593.
18. Kim NS, Im S, Kim SC. Dyschromatosis universalis here: an electron microscopic examination. *J Dermatol* 1997;**24**:161–4.
19. Frank J, Happle R. Cutaneous mosaicism: right before our eyes. *J Clin Invest* 2007;**117**:1216–9.