Eur J Pediatr (2000) 159: 745–749

ORIGINAL PAPER

Martino Ruggieri

Cutis tricolor: congenital hyper- and hypopigmented lesions in a background of normal skin with and without associated systemic features: further expansion of the phenotype

Received: 9 December 1999 and in revised form: 10 April 2000 / Accepted: 11 April 2000

Abstract The term cutis tricolor describes the uncommon co-existence of congenital hyper- and hypopigmented macules, in close proximity to each other, in a background of normal skin so far seen in a 17-year-old patient with various other congenital defects. The suggested explanation for this phenomenon is allelic twin spotting. We report on two boys, aged 6 and 11 years, with an unusual combination of three different degrees of pigmentation, one of whom had in addition, psychomotor delay, dysmorphic features, musculoskeletal abnormalities and subcortical and periventricular white matter high signal lesions on brain neuroimaging. In both cases a search for mosaicism in peripheral blood lymphocytes and cultured fibroblasts was negative. In contrast to the previously reported case, the two children had large streaks or patches of hyper- and hypopigmented skin lesions, in close proximity to each other, involving large areas of the body. The rest of the skin had a normal intermediate pigmentation.

Conclusion This combination of three degrees of pigmentation in association with systemic defects in one child and the lack of such association in the other confirms and further expands the clinical phenotype of cutis tricolor.

Introduction

Happle et al. [7] in a recently described new syndrome coined the term "cutis tricolor" for the presence of congenital hyper- and hypopigmented macules on a background of normal skin. The skin changes in their sporadic case were associated with multisystemic birth defects [7].

Here, two children are reported with an unusual combination of three degrees of pigmentation of whom one had, in addition, psychomotor delay, dysmorphic features, musculoskeletal abnormalities and white matter lesions on brain neuroimaging.

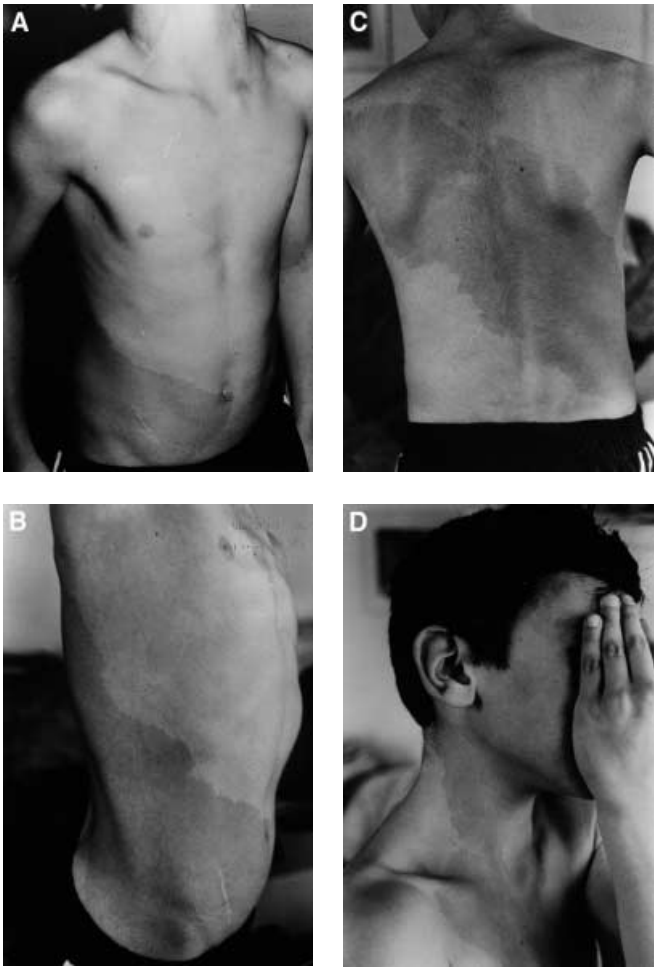
Case reports

Case 1

This 11-year-old boy was the full-term product of unrelated parents born after normal delivery following an uneventful pregnancy. Developmental milestones were normal. He was recalled to have since birth a large, circumferential, streaky segment of café-au-lait pigmentation over the trunk. At age 6 years, on the basis of the above lesion and of three additional café-au-lait spots, the diagnosis of neurofibromatosis type 1 (NF1) was suggested. At that time, screening investigations, including slit lamp and fundus examination, ECG, EEG, abdominal and heart ultrasound and brain MRI were normal.

When first referred to our institution at age 9 years, on examination his height, weight and head circumference were within the 50th percentile. There were no dysmorphic features. On examination of the skin, a peculiar pigmentary disturbance was noted (Figs. 1, 2). A large, spirally shaped, streaky hyperpigmented lesion involved the lower abdomen from the right peri-umbilical area, with a sharp midline cutoff, over the right flank and trunk across the interscapular region and the left scapular area under the axilla and around the left chest and neck towards the mandible and right cheek. In addition, well demarcated areas of hypopigmented streaks were present in the right upper chest (Figs. 1A,B, 2) and hypopigmented patches in the right supraclavicular area and neck (Figs. 1B, 2), in close proximity to the hyperpigmented lesions. The rest of the skin had a normal intermediate pigmentation (Figs. 1, 2). Three café-au-lait macules (1×2 cm across) with irregular borders, were noted over the trunk and left thigh. The rest of physical examination was otherwise unremarkable. Absence of

M. Ruggieri (✉)
Division of Paediatric Neurology, Department of Paediatrics, University of Catania, Via S. Sofia 78, 95125 Catania, Italy
e-mail: rupo@ctonline.it
Tel.: +39-095-256408; Fax: +39-095-222532



◀

Fig. 1A–D Case 1 at age 10 years. **A** A large streak of hyperpigmentation involves the lower abdomen from the right peri-umbilical area with a sharp midline cutoff. Note the hypopigmented area over the right upper chest in close proximity to the hyperpigmented lesion over the left upper chest and the normally pigmented skin over the upper portion of the abdomen. **B** The lesion goes over the right flank and trunk. Note the triple coloured skin: the right upper chest is hypopigmented, the upper portion of the abdomen is normally pigmented and the lower abdomen hyperpigmented. **C** Involvement of the posterior aspect of the trunk across the interscapular region and the left scapular area under the axilla. **D** Note the hyperpigmented lesion over the left chest, neck, the mandible and the right cheek. A well demarcated area of hypopigmentation is evident in the right supraclavicular area in close proximity to the hyperpigmented lesions. The rest of the skin has a normally pigmented background

NF1 and NF2 gene mutations using 15 NF1 polymorphic microsatellite markers [19] and the NF2 polymorphic microsatellite markers was demonstrated in the peripheral blood lymphocytes obtained from the proband and his relatives and in the cultured fibroblasts obtained from the proband's hyperpigmented and normal skin areas.

Case 2

A 6-year-old boy had psychomotor retardation, multiple dysmorphic features and widespread pigmentary disturbances. He was born at term after an uneventful pregnancy and normal delivery. His parents recalled that the pigmentary lesions were first noticed at age 3 months. When first referred to our institution he was 4 years old. On examination his height was >90th percentile and height and head circumference were within the 50th percentile. He had hypertelorism, epicanthal folds, deep set and forward rotated ears, deep nasal bridge, large and bulbous nose with broad nostrils, large philtrum and prominent lips and short neck (Fig. 3A). There was pectus excavatum (Fig. 3A), mild kyphoscoliosis resulting in scapular deformity (Fig. 3B) and leg length discrepancy with the

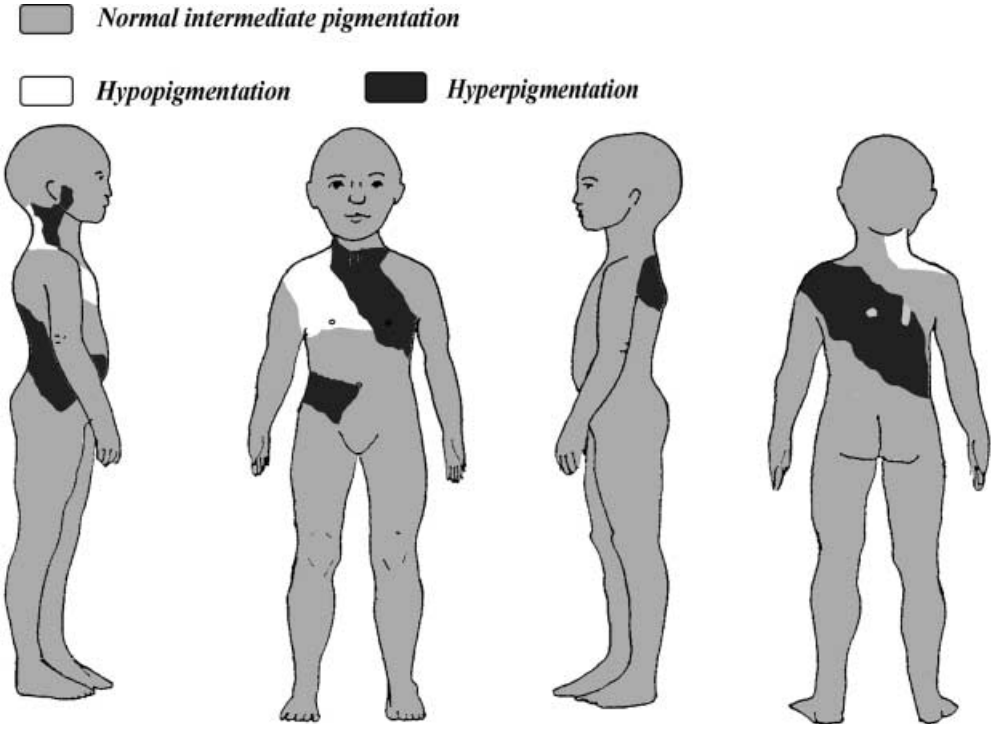


Fig. 2 Diagram showing the arrangement of the three different degrees of pigmentation in case 1

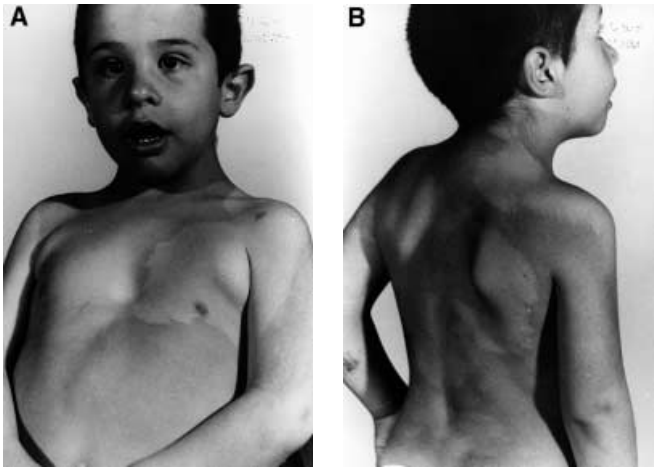


Fig. 3A, B Case 2 at age 4 years. **A** This shows hypertelorism, epicantal folds, deep set and forward rotated ears, a deep nasal bridge, a large and bulbous nose with broad nostrils, a large philtrum, prominent lips and pectus excavatum. Note the patches of hyperpigmented skin over the right chest and abdomen, the hypopigmented skin over the left chest and upper arm and the normally pigmented skin over the lower arm and forearm. **B** The neck is short and mild kyphoscoliosis results in scapular deformity. There are patches of hypopigmentation over the right scapular and shoulder regions in the posterior aspect in close proximity to the hyperpigmented lesions. The skin complexion is normally pigmented over the lower third of the arms and the forearms and the lumbar region

right leg being 1.5 cm shorter than the left leg. On examination of the skin there was a patchy pigmentary disturbance with multiple segmented areas of hyperpigmention involving the trunk and the limbs (Figs. 3, 4). These areas were alternated with well demarcated areas of hypopogmentation mostly over the left chest and the scapular region in the anterior aspect (Figs. 3A, 4) and the right scapular and shoulder regions in the posterior aspect (Figs. 3B, 4), in close proximity to the hyperpigmented lesions. Additional areas were present over the lateral aspect of the lower limbs (Fig. 4). The skin complexion was normal over the lower third of the arms and the forearms and the lumbar region (Figs. 3B, 4). The rest of physical examination was normal. Heart and abdominal ultrasonography were normal as were slit lamp and fundus examination. ECG and EEG gave normal results. Brain MRI scans revealed multiple, diffuse, non specific, subcortical and periventricular high signal lesions on T2-weighted images.

Morphological and cytogenetic analysis of the different skin areas

Punch biopsies were obtained from hyper- and hypopigmented skin areas and also from normal skin of both patients. Fibroblast cultures were established. Histologically, there was an increase in melanin content of the basal layer, but no dermal melanin or melanophages in the hyperpigmented areas and a decrease in the melanin content and in the number of melanocytes in the hypopigmented lesions. A normal epidermal and dermal architecture was present in the normally intermediate pigmented areas. Cytogenetic analysis of skin fibroblasts and peripheral blood lymphocytes (60 metaphases each; GTG banding technique, approximately 550 band stage) showed a normal 46, XY karyotype without any anomaly indicating mosaicism in both cases.

Discussion

In both the present cases the pigmentary lesions suggested genetic mosaicism [7]. In addition, the dysmorphic features and the neurological and musculoskeletal abnormalities seen in case 2 are frequently associated with chromosomal mosaicism [1, 4–6, 13, 14, 17]. In both cases mosaicism was excluded in the tissues analysed, however, normal peripheral blood or fibroblast cytogenetic studies do not exclude a mosaic state in another

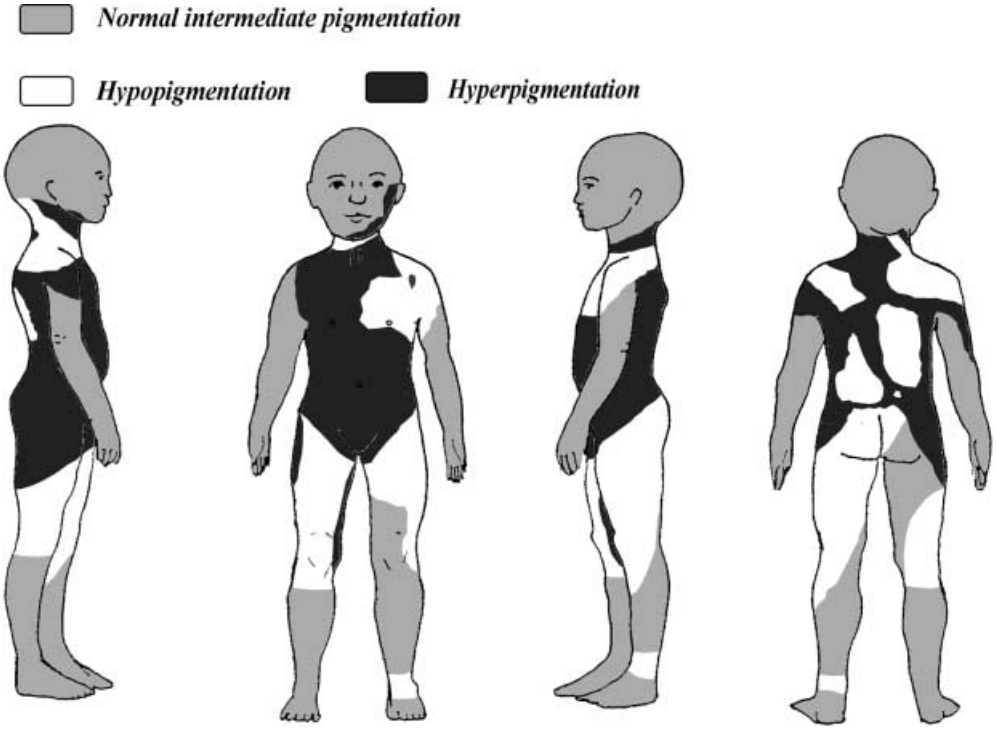


Fig. 4 Diagram showing the arrangement of the three different degrees of pigmentation in case 2

tissue (i.e., epidermal keratinocytes or melanocytes) or at the sub-chromosomal level [7, 10, 11, 13–15].

It could be argued that the pigmentary patterns reported here are either of the so-called type 1a pattern running in rather narrow bands along the lines of Blaschko, typically observed in the hypomelanosis of Ito phenotype or in incontinentia pigmenti of the Bloch-Sulzberger type, or of the type 1b pattern of broad bands seen in the McCune-Albright syndrome [4, 5]. However, in both children the skin anomalies were not typically distributed along the lines of Blaschko, histologically no incontinent pigment was seen in the dermis and, clinically, in both cases there were no preceding eruptive phases [1, 3–5, 13]. In addition, both cases were dissimilar from the McCune-Albright syndrome, a sporadic disorder manifesting with irregular and asymmetric brown pigmentary macules, most commonly seen over sacrum, buttocks or upper spine in association with polyostotic fibrous dysplasia and precocious puberty without additional hypopigmented areas [9, 15, 17]. Acquired Blasckolinear dermatoses, such as lichen striatus, linear psoriasis or linear lichen planus [1, 3, 13, 17, 20] were also ruled out because the skin abnormalities in both children were congenital, not preceded by erythematous and/or eruptive phases. Histologically there was a lack of spongiotic dermatitits (as seen in lichen), no hypogranulosis and orthokeratosis or parakeratosis (as seen in linear psoriasis), and, overall, the patients were different clinically [1, 13, 20, 22]. In addition, as both patients were boys, an X-linked dominant skin disorder was highly unlikely in so far as these conditions are thought to be lethal in males in whom no normal X chromosome is present to allow survival [5, 10].

In case 1 the spirally shaped pattern of the cutaneous pigmentary lesions was dissimilar to any of the known arrangements for human pigmentary mosaicism proposed by Happle [4, 5, 10], even though it could not be classified further. It was also dissimilar to the lesion patterns seen in patients affected by segmental NF1 [4–6, 12] (who are mosaic at the molecular level) [13, 16; Tinschert et al., personal communication, 2000] who have pigmentation anomalies only [16] and, histologically, differed from the (giant) café-au-lait spots seen in NF1 and NF2 which are composed of densely pigmented melanocytes [22]. NF1 and NF2 were also excluded by DNA analysis. Other hyperpigmented lesion patterns are seen in ring chromosome syndromes and in Schimke osseous dysplasia but these were ruled out on clinical and cytogenetic bases [5, 9, 15–17]. In case 2 the skin arrangement was also dissimilar from the so-called type 2 checkerboard pattern [4, 5] because there was lack of the alternating squares of pigmentary lesions arranged with a sharp midline separation, from the type 3 phylloid pattern [4, 5] because of lack of the oval or leaf-shaped patches arranged similarly to a floral ornament and from the type 4 patchy pattern without midline separation [4, 5] because the child's patchy pattern was not continuous in the midline aspect [4, 5, 10].

Notably, in the London Dysmorphology Database [21] there are 65 different syndromes under the entry "patchy pigmentary anomalies of skin" and in Smith's manual [9] the gamut list includes 48 conditions with "frequent" or "occasional altered skin pigmentation". These [9, 21], however, are well defined metabolic disorders or dysmorphic syndromes which were ruled out on clinical, laboratory and radiological grounds. Moreover, the pigmentary anomalies in these conditions are typical and well differentiated from the skin lesions in the present children [9, 21]. Further disorders ruled out were the so-called naevus depigmentosus in its isolated or segmental (for case 1) or systematised (for case 2) patterns with the typical block-like areas of hypopigmentation in the midline and the linear and whorled naevoid hypermelanosis in which there are multiple swirls or streaks of hyperpigmentation [1, 22]. Histologically the hypo- and hyperpigmented lesions in either condition are similar to the patterns seen in the present cases, however, here both pigmentary components were manifest at the same time.

Most likely, the combination of hyper- and hypopigmented skin lesions noted in both patients and the close spatial proximity of the two different birthmarks were not an incidental finding. In addition, these hyper- and hypopigmented patterns were associated with normally pigmented segments of skin and, therefore, a likely diagnosis might be that proposed by Happle et al. [7, 10] with the concept of "cutis tricolor". This newly described phenomenon has been tentatively explained by somatic recombination of two genetically different clones of neighbouring cells ("twin spotting") on a background of normal cells [7, 10, 20]. The phenomenon is well known in plants and animals and is widely used to test chemicals for their mutagenic or recombinogenic activity [7, 10]. Somatic recombination has been also observed in humans. The hypothesis was raised that the spatial and temporal proximity occurring in the so-called vascular twin naevi as well as their similarities to the twin spots observed in the animals and plants could also be explained by the mechanism of somatic recombination. Other skin disorders have been reported whose combination of pigmentary patterns was tentatively explained by the same genetic phenomenon [1, 2, 7–10, 18]. In contrast to the cases of Happle et al. [7], the pigmentary lesions in the present children were not confined to circumscribed body segments but involved extensive areas of the body. Thus, the pigmentary disturbance reported here resembles more that of other paired skin disorders possibly caused by the same mechanism of nonallelic twin spotting [1, 7, 10] such as phacomatosis pigmentovascularis [2, 5, 8] or phacomatosis pigmentokeratotica [18] where there is sometimes a simultaneous occurrence of three different mosaic skin lesions suggesting a combination of allelic and nonallelic twin spotting [1, 7, 10]. In the light of the previous reports [1, 7–10, 18, 20] and the present cases one could suggest that the pigmentary pattern in cutis tricolor could be due to somatic mutations and to the time of the mutation (early

versus late embryonic development). Thus, in the case reported by Happle et al. [7] a somatic mutation could have occurred later in embryogenesis leading to manifestations confined to a single site while in both the present cases an earlier mutation most likely led to disseminated manifestations.

The combination of these unusual skin pigmentary lesions with systemic defects in one child (case 2) and the lack of such association in the other (case 1) would further expand the overall phenotype of cutis tricolor [7, 10]. Clinicians will, in the future, probably notice further localised or systematised pigmentary patterns arranged in close proximity to each other which in turn might be explained as a twin spotting phenomenon [1, 7, 10].

Acknowledgements I wish to thank Professor G. Sorge for originally referring case 1, Professor L. Pavone (Catania) and Dr S.M. Huson (Oxford) for their helpful suggestions and discussion, Dr M. Crockney (Oxford) for performing cytogenetic analyses, Dr G. Magro (Catania) for morphological analysis of the skin biopsies and Dr M. Upadhyaya (Cardiff) for performing neurofibromatosis molecular analysis. Massimiliano Cascone, Servizio Elaborazione Immagini, CNR, Area della Ricerca di Catania, is gratefully acknowledged for his skilled technical assistance in preparing the illustrations.

References

1. Bolognia JL, Orlow SJ, Glick SA (1994) Lines of Blaschko. J Am Acad Dermatol 31: 157–190
2. De la Heras E, Boixeda JP, Ledo A, Happle R (1997) Paired melanotic and achromic macules in a case of phacomatosis pigmentovascularis: a further example of twin spotting? Am J Med Genet 70: 336–337
3. Grosshans EM (1999) Acquired Blaschkolinear dermatoses. Am J Med Genet 85: 334–337
4. Happle R (1993) Pigmentary patterns associated with human mosaicism: a proposed classification. Eur J Dermatol 3: 170–174
5. Happle R (1993) Mosaicism in human skin. Understanding the patterns and mechanisms. Arch Dermatol 129: 1460–1470
6. Happle R (1999) Loss of heterozygosity in human skin. J Am Acad Dermatol 41: 143–164
7. Happle R, Barbi G, Eckert D, Kennerknecht I (1997) "Cutis tricolor": congenital hyper- and hypopigmented macules associated with a sporadic multisystem birth defect: an unusual example of twin spotting? J Med Genet 34: 676–678
8. Hasegawa Y, Yasuhara M (1985) Phakomatosis pigmentovascularis type IVa. Arch Dermatol 121: 651–655
9. Jones KL (1997) Smith's recognisable patterns of human malformations, 5th edn. Saunders, Philadelphia
10. Koopman RJJ (1999) Concept of twin spotting. Am J Med Genet 85: 355–358
11. Moss C (1999) Cytogenetic and molecular evidence for cutaneous mosaicism: the ectodermal origin of Blaschko lines. Am J Med Genet 85: 330–333
12. Moss C, Green SH (1994) What is segmental neurofibromatosis? Br J Dermatol 130: 106–110
13. Moss C, Savin J (1995) Dermatology and the new genetics. Blackwell, Oxford
14. Moss C, Larkins S, Stacey M, Blight A, Farndom PA, Davison EV (1993) Epidermal mosaicism and Blaschko's lines. J Med Genet 30: 752–755
15. Paller AS (1996) Pigmentary patterning as a clinical clue of genetic mosaicism. Arch Dermatol 132: 1234–1235
16. Ruggieri M (1999) The different forms of neurofibromatosis. Childs Nerv Syst 5: 295–308
17. Sybert VP (1997) Genetic skin disorders. Oxford University Press, New York
18. Tadini G, Restano L, Gonzales-Perez I, Gonsales-Ensenat A, Vincente-Villa MA, Cambiaghi S, Marchettini P, Mastrangelo M, Happle R (1998) Phacomatosis pigmentokeratotica: report of a new case and further delineation of the syndrome. Arch Dermatol 134: 333–337
19. Upadhyaya M, Ruggieri M, John M, et al. (1998) Gross deletions of the neurofibromatosis type 1 gene (Nf1) are predominantly of maternal origin and commonly associated with a learning disability, dysmorphic features and developmental delay. Hum Genet 102: 591–597
20. Various Authors (1999) Mosaicism in human skin. Proceedings of a symposium in honour of Rudolf Happle. Marburg, Germany, May 1998. Am J Med Genet 85: 323–364
21. Winter RM, Baraitser M (2000) The London dysmorphology database. Oxford University Press, Oxford
22. Zvulunov A, Esterly NB (1995) Neurocutaneous syndrome associated with pigmentary skin lesions. J Am Acad Dermatol 32: 915–935