Original Article

Cutis tricolor: a literature review and report of five new cases

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Background: *Cutis tricolor* is a skin abnormality consisting in a combination of congenital hyper- and hypopigmented skin lesions (in the form of paired macules, patches or streaks) in close proximity to each other in a background of normal skin. It is currently regarded as a twin-spotting (mosaic) phenomenon and today is clear that not all cases of cutis tricolor represent one single entity. This phenomenon has been reported so far either: (I) as an purely cutaneous trait; (II) as a part of a complex malformation phenotype (*Ruggieri-Happle syndrome*, RHS) including distinct facial features, eye (cataract), skeletal (skull and vertebral defects, and long bones dysplasia), nervous system (corpus callosum, cerebellar and white matter anomalies, cavum vergae and holoprosencephaly) and systemic abnormalities; (III) as a distinct type with multiple, disseminated smaller skin macules (*cutis tricolor parvimaculata*); and (IV) in association with other skin disturbances [e.g., cutis marmorata telangectasica congenita (phacomatosis achromico-melano-marmorata)] or in the context of other skin (e.g., ataxia-telangiectasia and phacomatosis pigmentovascularis, PPV) or complex malformation phenotypes (e.g., microcephaly and dwarfism).

Methods: (I) Review of the existing literature; and (II) information on our personal experience (clinical, laboratory and imaging data) on new cases with *cutis tricolor* seen and followed-up at our institutions during years 2010–2016.

Results: The existing literature revealed 19 previous studies (35 cases) with pure cutaneous or syndromic cutis tricolor phenomena. Our personal experience included 5 unpublished patients (3 boys; 2 girls; currently aged 2 to 14 years) seen and followed-up at our Institutions in Italy who had: (I) skin manifestations of the cutis tricolor type (N=5); (II) skeletal abnormalities including small skull (n=2), obtuse angle of mandible (n=3), mild to moderate scoliosis (n=3), vertebral defects (n=3), and long bones bowing (n=3); mild psychomotor delay (n=3); epilepsy (n=2); anomalies of the corpus callosum (n=3); and cavum vergae (n =2).

Conclusions: This study further confirms and expands the overall phenotype of cutis tricolor. By literature review and personal experience we conclude that the skin abnormalities of the cutis tricolor type are stable over time; the skeletal defects are mild to moderate and do not progress or cause relevant orthopaedic complications; the neurological/behavioural phenotype does not progress and the paroxysmal events (when present) tend to decrease over time; there is a typical facial phenotype in some patients (long, elongated face, thick and brushy eyebrows, hypertelorism, deep nasal bridge with large bulbous nose and anteverted

nostrils), which characterizes a somewhat distinct syndromic phenotype; some patients may develop early onset cataracts. The allelic dydymotic hypothesis of post-zygotic mutations likely involving the same gene loci could well explain the overall skin, bone, lens and nervous system phenomena of migration of different streaks of clones in the different tissues.

Keywords: Cutis tricolor; *Ruggieri-Happle syndrome* (RHS); mosic; mosaicism; skin; neurological; imaging; magnetic resonance imaging (MRI)

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Introduction

The term *cutis tricolor* describes the combination of congenital hyper- and hypopigmented lesions (in the form of macules, patches or streaks), in close proximity to each other, in a background of normal skin (1-20). This phenomenon has been reported so far either (18): (I) as an *purely cutaneous trait* (3,5,7,11,17,18); (II) as a part of a complex malformation phenotype (*Ruggieri-Happle syndrome*, RHS) (18,21-23) including distinct facial (a peculiar facial phenotype consisting in coarse, asymmetric and later in adolescence elongated face, thick and brushy eyebrows, hypertelorism, deep nasal bridge with large bulbous nose and anteverted nostrils, low-set ears, large phyltrum), eye (congenital cataract), skeletal (small skull, dystrophic vertebrae, and mildly bowed long bones), nervous system [corpus callosum anomalies, white matter abnormalities (i.e., delayed myelination), holoprosencephaly and cerebellar anomalies] and systemic abnormalities (2,3,6,8,11-14,16,18,19); (III) as a distinct type with multiple, disseminated smaller skin macules (*cutis tricolor parvimaculata*) (9,15,18) [different from the autosomal dominant congenital hypo- and hyperpigmented macules (Westerhof syndrome; MIM # 154000)]; and (IV) in *association* with *other skin disturbances* [e.g., cutis marmorata telangectasica congenita (phacomatosis achromico-melano-marmorata)] or in the context of other skin disorders (e.g., ataxia-telangiectasia and phacomatosis pigmentovascularis, PPV) or neurocutaneous phenotypes (4,10,13,20).

Cutis tricolor has been postulated to represent a twin-spotting phenomenon (18,24-26). Paradominant inheritance has been postulated as a possible mechanism (22) to explain familial occurrence as in the case of Baba *et al.* (5) who reported a pure skin phenotype of the "cutis tricolor" type in two sisters.

In 1997 Happle and co-workers coined the term "*cutis tricolor*" for the unusual combination of three degrees of skin pigmentation in close proximity to each other. In their 17-year-old boy they described congenital hyper- and hypopigmented macules confined to circumscribed body segments on a background of normal intermediate skin complexion in association with multiple birth defects (2). Ruggieri (3) subsequently expanded the cutaneous phenotype by including cases with abnormal paired pigmentation in the form of large patches (in the form of a yet unclassified archetypical pattern of cutaneous mosaicism) (1,23,26-28) or streaks (sash-like pattern of cutaneous mosaicism) (1,23) diffusely involving the body associated (case 2) (3) or not (case 1) (3) to systemic defects. The spectrum of extra-cutaneous manifestations further expanded in recent years including specific facial dysmorphic, skeletal and brain abnormalities (6,11-14,16,19).

Pure cutaneous traits (3,5,7,11,17) and variant forms have been also reported (9,15) and the skin anomaly has been recorded within the context of well-known and less well-known phenotypes (4,10,20).

Suggested eponyms for the complex malformation syndrome with cutis tricolor have been cutis tricolor syndrome (1,21) or RHS (1,18,21-23).

Methods

Patients

The Unit of Rare Diseases of the Nervous System in Childhood at the University of Catania, Italy, has been established in 2016 (formerly—since 1992—Unit of Paediatric Neurology) and caters to children and their families with different neurologic disorders in the paediatric age group (including neurocutaneous diseases), which are referred for diagnosis, management advice, and genetic counselling from the southern, central, and eastern Sicilian region (i.e., the towns and provinces of Catania, Siracusa, Ragusa, and Enna, with an approximate population of 1.9 million inhabitants out of the 5.8 million inhabitants of Sicily). Subjects are referred from all the city hospitals,

the general paediatricians, and general practitioners, the regional lay group associations, and the consultants in dermatology, paediatrics, neurology, ophthalmology, radiology, and genetics in the regions. The hospitals, the lay groups, and the practitioners and consultants are contacted annually via letters for their needs of referrals.

Following our reports of 2010–2011 (13,14)—between 2010 and 2016—patients with *cutis tricolour* were diagnosed and followed-up at our institution in Catania. All these patients underwent a full clinical evaluation and laboratory investigation at the time of the initial diagnostic work-up and re-investigated at the follow-up visits.

The diagnosis of *cutis tricolour* was based on the following: the presence of hyper- and hypo-pigmented skin abnormalities in the form of macules, patches, or streaks in close proximity to each other on a background of normal skin.

The general and neurologic status was assessed during first referral and follow-up visits by means of standard clinical evaluations and neuropsychological testing.

Magnetic resonance imaging (MRI) studies were performed on a 1.5 T Philips Gyroscan and electroencephalography (standard EEG and video-EEG) was also performed in the presence of a clear or suspect neurologic anomaly at diagnosis and during follow-up.

In all patients, a standard and array-CGH analysis was performed.

Literature review

Studies published in the literature (Medline, Scopus, WOS and bibliographies) reporting on cutis tricolor and/or conditions associated to skin phenomena of the cutis tricolor type in association or not with systemic/neurological involvement were reviewed (all years). Literature search was performed by using the following key words: "*cutis tricolor*", "*twin spotting*", "*skeletal*", "*bone*", "*neurological*", "*nervous system*", and "*MRI*": were considered studies reporting data in English, German, French and Spanish.

Results

Patients

Our personal experience included five unpublished patients (3 boys; 2 girls; currently aged 2 to 14 years) first seen and followed-up at our Institutions by means of the above methods.

The clinical, laboratory, and imaging findings of these five patients studied are summarised in *Tables 1* and *2*.

Literature review

The existing literature revealed 19 previous studies (2-20) for a total number of 35 cases with purely cutaneous traits (3,5,7,11,17,18) and with a combination of paired skin phenomena of the cutis tricolor type and associated cutaneous/systemic/neurological manifestations (2-4,6,8-14,15-23).

Discussion

By literature review (2-20) and personal experience (*Tables 1,2*) we have recorded 40 cases so far with the following demographic, clinical, laboratory and imaging features and natural history.

Incidence and prevalence

In the recorded cases [(2-20); and *Tables 1,2*] there were no significant sex and race differences (18), even though the figures are too low to draw demographic conclusions.

Clinical manifestations

The hallmarks of disease are the paired skin anomalies. Here below we summarises the main cutaneous and extra-cutaneous manifestations including imaging abnormalities.

Skin manifestations

These consist in the combination of hypopigmented and hyperpigmented anomalies in close proximity one to each other in a background of normal complexion (*Figure 1*). There is a wide variety of juxtaposed cutaneous lesions including macules, patches, and streaks, arranged in different archetypical (e.g., patchy, linear, sash-like, diffuse) (*Figure 1A*) (1,23,26) or less-well defined (unclassifiable) (*Figure 1B*) patterns (1,23,26) over confined or large body areas. The hallmark of the skin anomaly is: (I) the close spatial proximity of the two different birthmarks (*Figure 1*); and (II) the coexistence of three different complexions, which reflects the twin-spotting phenomenon (*Figure 1A,B*) (see below). Lesions usually manifest at birth or in the first months of life. The degree and (more rarely) the extent of the pigmentary anomaly can increase in the first years of life: then they stabilise and could also revert to normal or near-normal colour in some areas.

Facial phenotype

In the most severely affected cases (1,3,6,16) the face is coarse and mildly asymmetric with dolichocephaly and prominent

Table 1 Clinical findings in five cases with cutis tricolor syndrome

Main features	1	2	3	4	5
Sex	Male	Female	Female	Male	Male
Age	2	4	12	13	14
Clinical manifestations					
Height	25th	50th	95th	75th	50th
Weight	50th	50th	97th	97th	50th
OFC	25th	50th	98th	25th	50th
Cutis tricolor (pattern)	L, P	P	L, P	P	M
Face	+	–	–	+	–
Trunk	+	+	+	+	+
Upper limbs	–	+	+	–	–
Lower limbs	+	+	+	+	–
Coarse face	+	–	+	+	–
Facial asymmetry	+	–	+	+	–
Dolichocephalism	+	–	–	+	
Frontal bossing	+	–	+	+	–
Orbital bossing	+	–	+	+	–
Brushy eyebrows	+	+	+	+	+
Hypertelorism	+	–	+	+	–
Epicanthus	+	–	–	+	–
Deep nasal bridge	+	–	+	+	–
Large/bulbous nose	+	–	+	+	–
Large/anteverted nostrils	+	–	–	+	–
Low set ears	+	–	–	+	–
Posteriorly angulated ears	+	–	–	+	–
Wide philtrum	+	–	+	+	–
Prominent/thick lips	+	–	–	+	–
Prominent chin	+	+	+	+	–
Clinodactyly	+	+	+	–	–
Short neck	+	+	+	+	–
Pectus excavatum	+	+	+	+	+
Developmental milestoned	D	N	D	D	N
Hypotonia	+	–	+	+	–
Poor co-ordination	+	–	–	–	–
Language	D	N	D	D	N
Epilepsy	–	–	–	+	+
Onset	NA	NA	NA	6y	2y
Seizure type	NA	NA	NA	GTCS	GTCS
Outcome/age ceased	NA	NA	NA	9y	11y
Behavioural anomalies	+	–	–	+	+
Mental retardation	Mo	–	Mi	Mo	Mi
Other	–	–	Cataract	–	VSD

OFC, occipitofrontal circumference; L, linear; P, patches; M, multiple maculae; +, present; –, absent; N, normal; D, delayed; NA, not applicable; y, years; GTCS, generalised tonic clonic seizures; Mi, mild; Mo, moderate; Se, severe; VSD, ventricular septal defect.

Table 2 Laboratory and imaging findings in five cases with cutis tricolor syndrome

Main features	1	2	3	4	5
Sex	M	F	F	M	M
Age	2	4	12	13	14
Radiographic feature					
Small skull	+	–	–	+	–
Prognathism	+	–	+	–	–
Obtuse angle of mandible	+	–	+	+	–
Absent posterior arch atlas	+	–	–	–	–
Scoliosis	+	–	+	+	–
Cervical	+	–	–	–	–
Thoracic	+	–	+	+	–
Lumbar	–	–	+	+	–
Kyphosis	+	–	+	+	–
Lordosis	+	–	+	+	–
Vertebral scalloping	+	–	+	+	–
Increased distance pedicles	+	–	+	+	–
Altered pedicles	+	–	+	+	–
Metaphyseal osteosclerosis	–	–	–	+	–
Rib abnormalities	+	–	+	+	–
Bowing of long bones	+	–	+	+	–
Upper limbs	–	–	–	–	–
Lower limbs	+	–	+	+	–
Leg length discrepancy	+	–	+	+	–
Neuroimaging features					
Asymmetric ventricles	+	–	+	–	–
White matter anomalies	+	–	–	+	–
Corpus callosum anomalies	+	–	+	+	–
Laboratory findings					
EEG abnormalities	+	–	+	–	–
Cytogenetic analysis					
Array-CGH (anomalies)	–	–	–	–	–

M, male; F, female; +, present; –, absent; NP, not performed; EEG, electroencephalography; CGH, comparative genomic hybridization.

metopic suture; there is orbital bossing, thick and brushy eyebrows, hypertelorism, mild epicanthus, deep nasal bridge with large, bulbous nose and anteverted nostrils; low set and anteriorly rotated ears; large phyltrum and thick lips; the palate is narrow with small and spaced teeth; the chin is prominent. In our experience [(3,6,16), *Table 1*], at birth—in the cases with facial dysmorphisms—the face could present only with a minor (minimal) degree of dysmorphisms: then, over the years, mostly across the pre-pubertal and pubertal period, the face tends to elongate and to thin, and the nasal features become more prominent (3,6,16).

Eye findings

In one study (12), three children with syndromic cutis tricolor developed moderately to large sized, dense (with thick fibrosis under the anterior capsule), cortical-nuclear and subcapsular, monocular to binocular cataracts. Their ages at diagnosis of cataracts was comprised between 11 and 14 to 15 years. They did not develop other manifestations in the anterior or posterior segments. All were successfully operated with

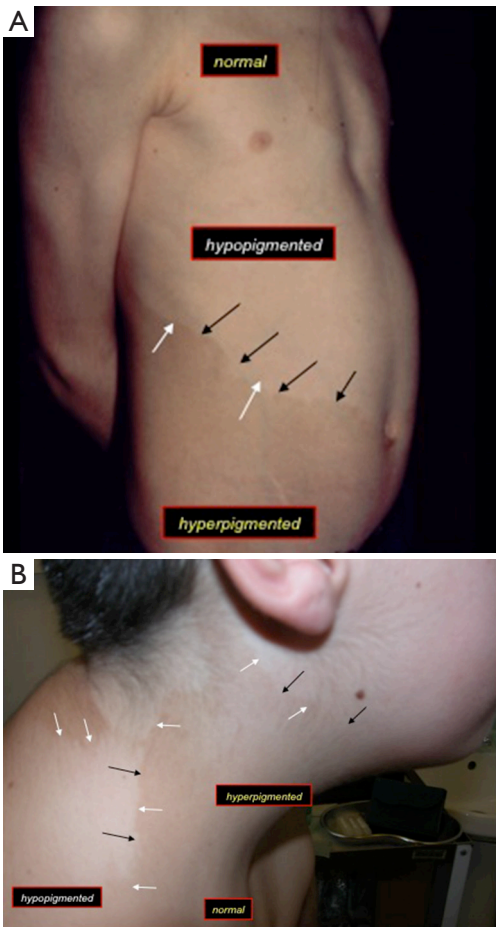

Figure 1 Close view-up of the skin in two children with cutis tricolor: as a pure trait (A) in an archetypical sash-like (spiral) pattern of mosaic distribution [case 2 in (3)]; and (B) as a complex malformation phenotype in a less-well defined/unclassifiable mosaic pattern of distribution [case 1 in (3)]. Note the hyperpigmented (the "hyperpigmentation" is pointed by the black arrows) and hypopigmented (the "hypopigmentation" is pointed by the white arrows) areas in close proximity one to each other in a background of normal complexion (labelled as "normal").

normal postoperative eye examinations. At gross pathology and histopathological examination there were eosiphilic large fibres arranged in two to multiple streaks with vacuolisation of superficial cortical fibres and extracellular clefts (12). The cataracts were classified as syndermatotic anterior polar cataracts, which usually are associated to dermatologic conditions (12). In the present study, two additional patients (cases 3 and 4; *Table 1*) had cataracts with similar features to those previously recorded (12).

Skeletal abnormalities

The radiographic features in the syndromic patients so far analysed (2,3,6,8,11-14,16,18,19), include [reviewed in (14)]: a small skull (not microcephalic) with prognathism; the pituitary fossa can be "J" shaped and abnormally shaped (*Figure 2A*) with implanted teeth sprouts and numerous dental cysts; absent posterior arch of the atlas; obtuse angle of the mandible; scoliosis of different degrees and location (with additional lordosis and kyphosis: the abnormal curvature of the spine can be dystrophic in appearance, right-sided lower thoracic (T10–12) and upper lumbar (L1–3) with asymmetric peduncles and sloping ribs (n=6) or left- and right-sided upper thoracic (T4–T7) and lower lumbar (L1–L4) (*Figure 2B*); metaphyseal osteosclerosis of the femurs; mild to moderate bowing of long bones (*Figure 2C*). There is also clinodactyly of the fifth fingers.

Notably, the skeletal dysplasia (29) observed in syndromic patients with skin manifestations of the cutis tricolor type was reminiscent of neurofibromatosis type 1 (29), even though to a lesser degree: the scoliotic changes were milder than that encountered in NF1, the mandibular thinning and vertebral scalloping was not so pronounced, and the tibiae were bowed to a lesser extent than that usually seen in NF1 (29).

Bone age is usually mildly to moderately increased.

Neurological phenotype

In syndromic individuals [(2,3,6,8,11-14,16,18,19); and also *Table 1*], it consisted in [reviewed in (13)]:

(I) Mild hypotonia (3,6,13,16);

(II) Psychomotor delay with mild to moderate or (less frequently) severe cognitive delay [mean full-scale IQ in the syndromic cutis tricolor population (i.e., RHS) was 82.3 (range, 50–110): i.e., lower than the general population ($P<0.05$)] (3,6,13,16);

(III) Specific expressive language disabilities (non-progressive delay in production of *speech* sounds, communication milestones, and expressive language disabilities: improvement was attained after placement in special and early pre-school intervention programs) (3,6,13,16);

(IV) Epilepsy (i.e., generalised tonic-clonic or partial types first occurring between 18 months and 11 years of age);

(V) EEG abnormalities consisted in non-specific spike and wave activity in the centro-temporal and fronto-centro-temporal regions; occipital P and PO waves; and a Rasmussen-like pattern in one

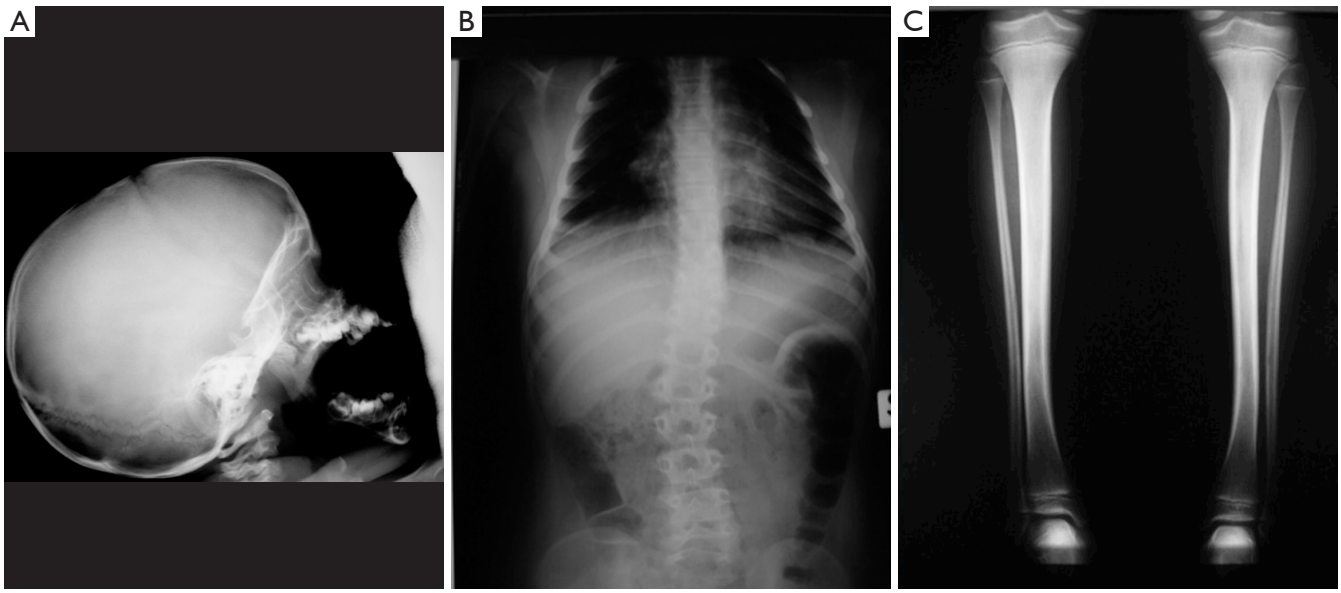

Figure 2 Radiographic abnormalities in three children with syndromic cutis tricolor: lateral view of the skull (A) showing a small skull (not microcephaly) with prognathism and "J" shaped pituitary fossa; antero-posterior view of the spine (B) showing an abnormal (dystrophic) curvature of the spine; antero-posterior view of the lower limbs (C) revealing mild bowing of the tibiae.

case [(13): who showed at age 2 years an initial diffuse paroxysmal activity with diffuse slowing and later developed hemispheric slowing activity with a typical Rasmussen type recording];

(VI) Altered behaviour [e.g., aggressive, violent and opposite behaviour, ADHD, obsessive-compulsive and autistic-spectrum like disorders: there was a recognisable *behavioural phenotype* in one study (13), consisting in an early (<5 years of age) phenotype of normal social interaction and eye-to-eye contact with temper tantrum episodes and frequent intense biting of objects, which evolved into obsessive-compulsive disorder or ADHD coupled with aggressive, opposite and near violent behaviour in toddler ages and aggressive behaviour with autistic spectrum disorder-like abnormalities after puberty and during adolescence into young adulthood];

(VII) Mood disorders.

Brain imaging abnormalities

Brain MRI studies revealed so far (2,3,6,8,11-14,16,18,19), multifocal, diffuse, confluent, bright signal abnormalities in the posterior periventricular (and subcortical) white matter on T2-weighted images (*Figure 3*). Other isolated imaging abnormalities were dilatation of the cerebral lateral ventricles and dysmorphisms/dysplasia of the corpus callosum (*Figure 4A*) with cavum vergae (*Figure 4B,C*), holoprosencephaly and brain teratoma (19). Studies of the spinal cord yielded normal findings in all the 14 subjects in one study (13).

Pathology

Punch biopsies collected from the involved areas showed histologically (2) 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. Electron microscopy showed (11): (I) in the hypopigmented area basal keratinocytes containing isolate melanosomes, some of them displaying an incomplete maturation; and (II) in the hyperpigmented area basal keratinocytes filled of mature melanosomes.

Molecular genetics and pathogenesis

A tentative genetic explanation of this postulated new phenotype could be a post zygotic somatic mutation (*Figure 5*) (1,22,23): loss of heterozygosity for the underlying mutation at an early developmental stage would give rise to

a complex malformation mosaic pattern (e.g., generalised skin manifestations of the cutis tricolor type in association to extra-cutaneous anomalies) as in the original case of Happle *et al*. (1) and in the subsequent studies reporting on syndromic phenotypes (2,3,6,8,11-14,16,18,19); post zygotic recombination occurring later during embryogenesis would give rise to pure cutaneous traits (i.e., manifestations confined to the skin only) (3,5,7,11,17,18) or to the distinct type of cutis tricolor parvimaculata (9,15,18). Non-allelic didymosis (22,23) would explain the coexistence of segmental lesions of pigmentary (e.g., paired hypo- and hyper-pigmented macules) and vascular (e.g., cutis marmorata telangiectatica) disturbance (4,10,13,20). Paradominant inheritance has been postulated (1,2,23) as a possible mechanism to explain familial occurrence as in the case of Baba *et al*. (5) who reported an isolated skin phenotype of the "cutis tricolor" type in two sistrs.

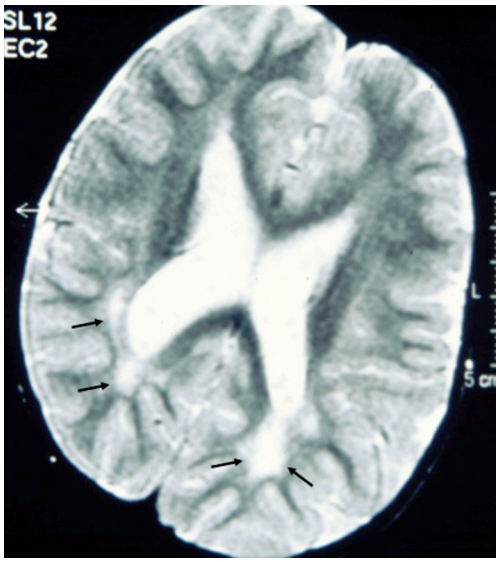

Figure 3 Axial T2-weighted magnetic resonance images of the brain in a child with syndromic cutis tricolor showing high signal lesions in the posterior (peritrigonal) white matter (black arrows): thes hyperintensities were recorded at age 6 years and regarded as delayed myelination.

Conclusions

This study further confirms and expands the overall phenotype of cutis tricolor. The skin abnormalities of the cutis tricolor type are usually stable over time and do not benefit pf sophisticated laser therapeutic techniques; the skeletal defects are mild to moderate and do not progress or cause relevant orthopaedic complications; the neurological/behavioural phenotype and the paroxysmal events (when present) tend to stabilise over time [seizures can be treated similarly to those in patients without cutis

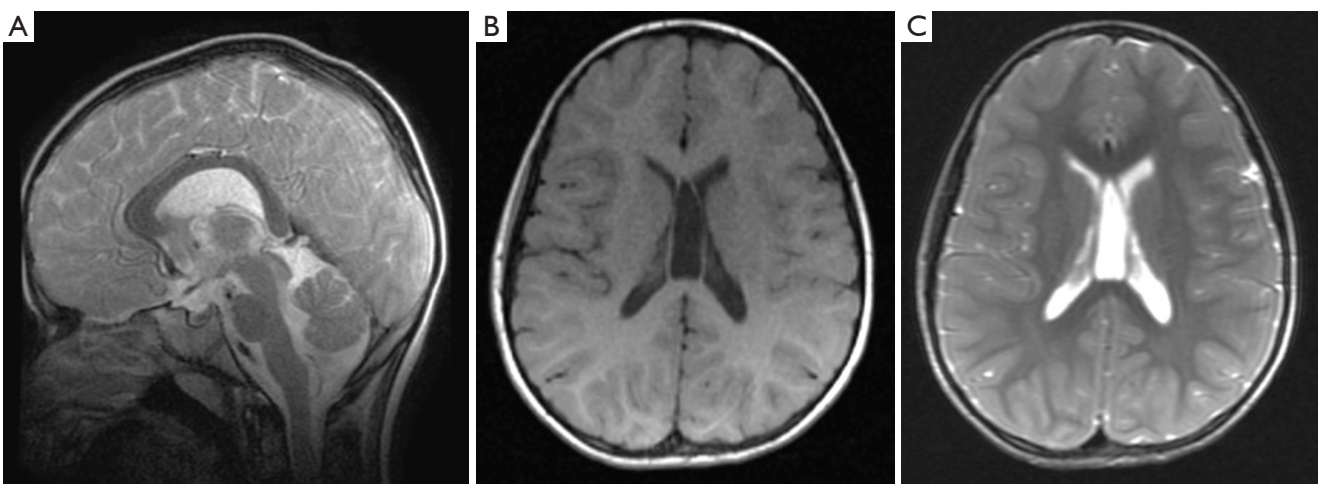

Figure 4 Sagittal T2-weighted (A) magnetic resonance imges of the brain in a child with syndromic cutis tricolor reveals a dysmorphic corpus callosum; axial T1- (B) and T2-weighted (C) magnetic resonance images of the brain in a child with syndromic cutis tricolor showing a cavum vergae.

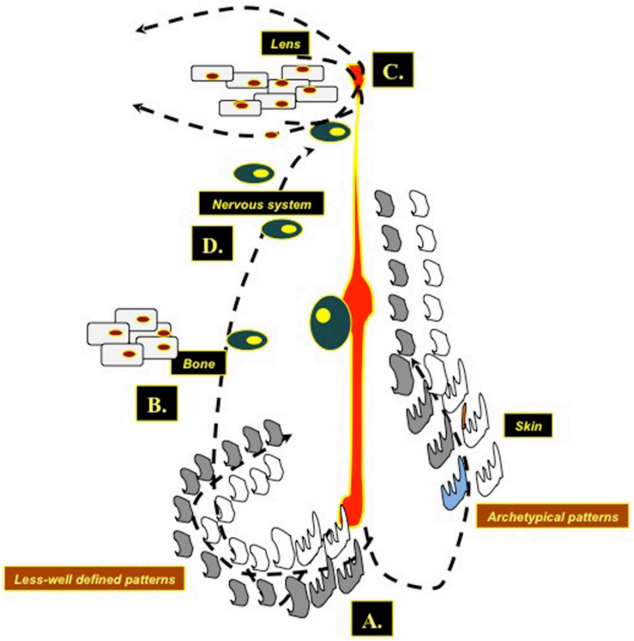

Figure 5 Drawing illustrating the *unifying* (*allelic*) *dydymotic theory* as a pathogenic explanation for the cutis tricolor phenotypes: (A) a post zygotic somatic mutation leading to heterozygosity for the underlying yet undiscovered gene responsible for the skin anomaly at an early developmental stage would give rise to a complex malformation mosaic pattern (e.g., syndromic cutis tricolor) whilst, at a later embryonic stage would give rise to pure cutaneous traits (i.e., manifestations confined to the skin only) or to the distinct type of cutis tricolor parvimaculata. These heterozygous cutaneous cell populations (grey and white cells in the figure) can generate in the skin (A) either archetypical or less-well defined mosaic patterns. Similar phenomena occur in the bone (skeletal abnormalities) (B), in the lenses (C) [note the different populations of cortical-subcortical lens cells migrating in parallel streaks [as found at histopathology in the cataracts of children with cutis tricolor, see (12)], and in the nervous system (D), generating layers disarraying in the subcortical white matter leading to delayed myelination or to clones of disordered neuronal cells.

tricolor phenomena: some patients with intractable seizures benefited of combination of antiepileptic drugs]; problems at school may need special help and stimulants drugs associated with antiepileptic treatment. notably, a typical facial phenotype in some patients could help the diagnostic work-up as it characterizes a somewhat distinct syndromic phenotype; some patients may develop childhood cataracts.

Paired skin phenomena of the cutis tricolor type are likely more frequent than previously thought and should be investigated (when dictated by clinical findings) by means of: (I) brain and spinal cord MRI studies; (II) skeletal X-ray studies; (III) systemic (i.e., heart, abdominal and pelvic) ultrasound studies; (IV) neurophysiologic studies (EEG); (V) psychomotor testing; (VI) and routine laboratory investigation.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflict of interest to declare.

Ethical Statement: This study was approved by the local ethics committee (*Comitato Etico 1*, University of Catania). Patients' consent was obtained (and/or waived due to the non-interventional retrospective analysis nature of this study).

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