GENETIC HYPOMELANOSIS

Generalized hypomelanosis

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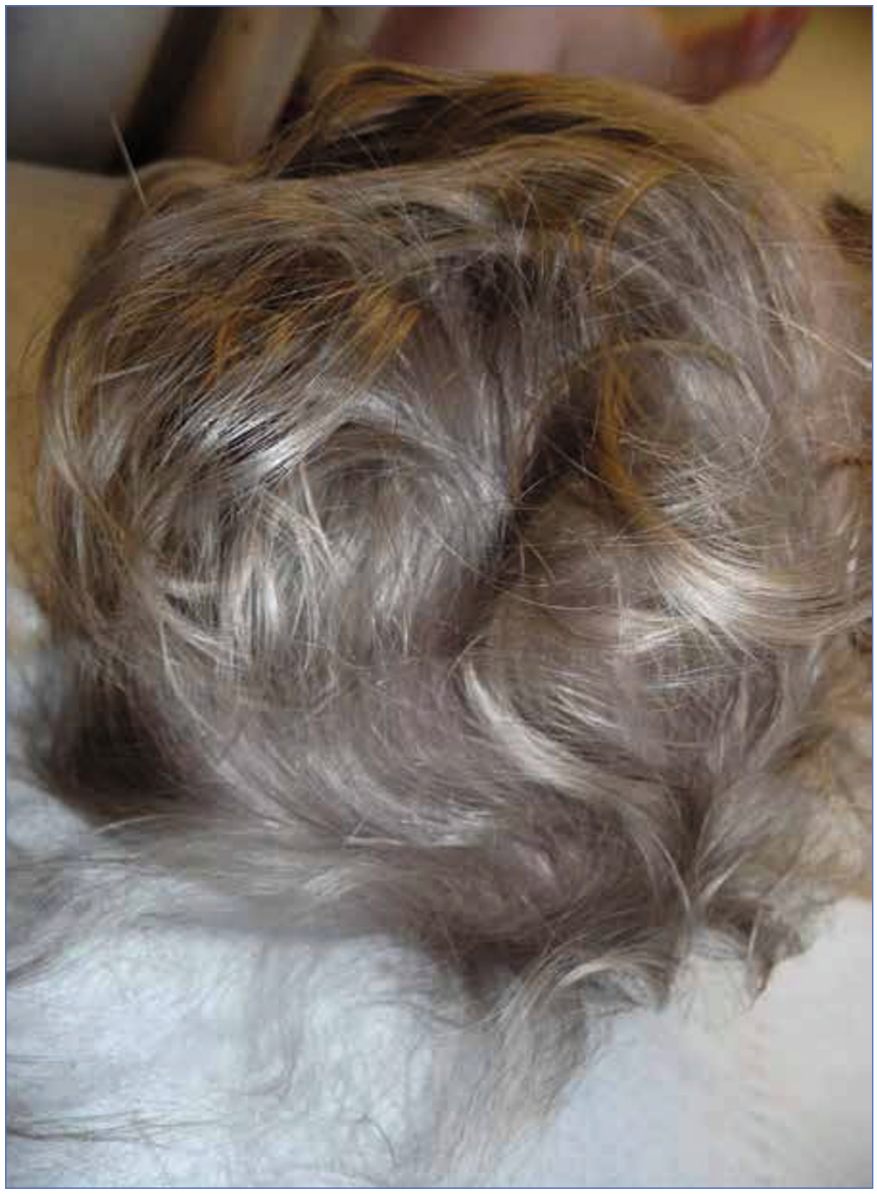
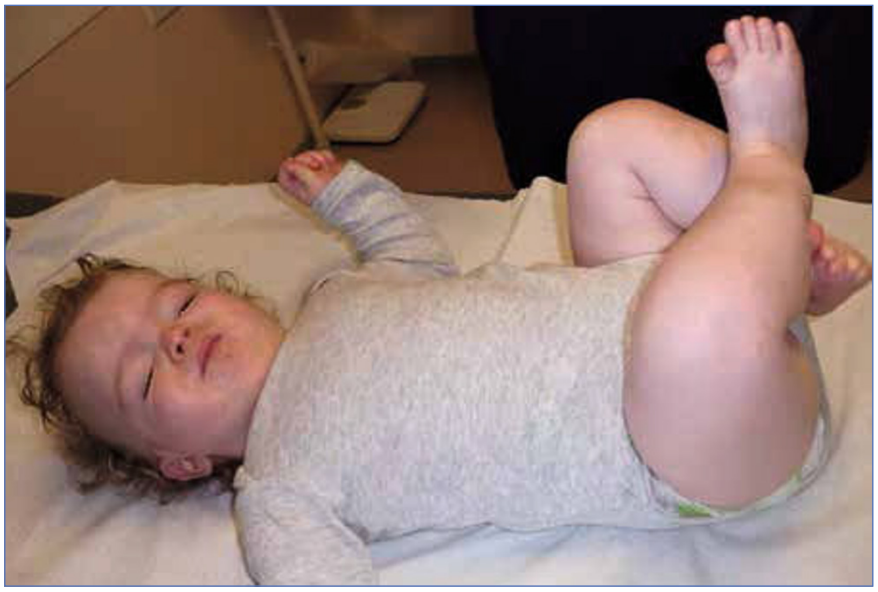
CHEDIAK-HIGASHI SYNDROME



Silvery hair in a child with Chediak-Higashi syndrome.



Pigmentary dilution of the skin in a child with Chediak-Higashi syndrome (his parents are skin type IV).

OMIM: #214500

GENETICS
Autosomal recessive inheritance with mutations in the LYST gene (1q42.3).

MOUSE MODEL
Beige.

EPIDEMIOLOGY
Rare autosomal recessive disorder.

PATHOPHYSIOLOGY
LYST, a cytoplasmic protein, is a key trafficking lysosomal regulator. It results in defective membrane targeting of the proteins present in secretory lysosomes.

CLINICAL DERMATOLOGICAL PRESENTATION
Pigmentary dilution of the skin (as to be compared with unaffected first-degree relatives).
Silvery hair.

EXTRACUTANEOUS SIGNS
Ocular hypopigmentation, photophobia, nystagmus and reduced visual acuity.
Bleeding diathesis due to diminished function of platelet dense granules.
Progressive neurologic dysfunction.
Severe immunodeficiency due to abnormal lytic granules in lymphocytes, NK cells and neutrophils.

HISTOPATHOLOGY
Presence of giant melanosomes within melanocytes due to the uncontrolled fusion of not only melanosomes but also other lysosome-derived organelles (giant lysosomes within neutrophils are also observed in the serum).

DIFFERENTIAL DIAGNOSIS
- Griscelli syndrome.
- Hermansky-Pudlak syndrome.
- Oculocutaneous albinism.

TREATMENT
Death often occurs during childhood due to infection, to gastrointestinal hemorrhage, or to lymphoproliferative syndrome known as the 'activated phase'.
Bone marrow transplant should be proposed early if possible. High doses of methylprednisolone have been used to treat the 'activated phase'.
Antibiotics and antivirals.

KEY REFERENCES

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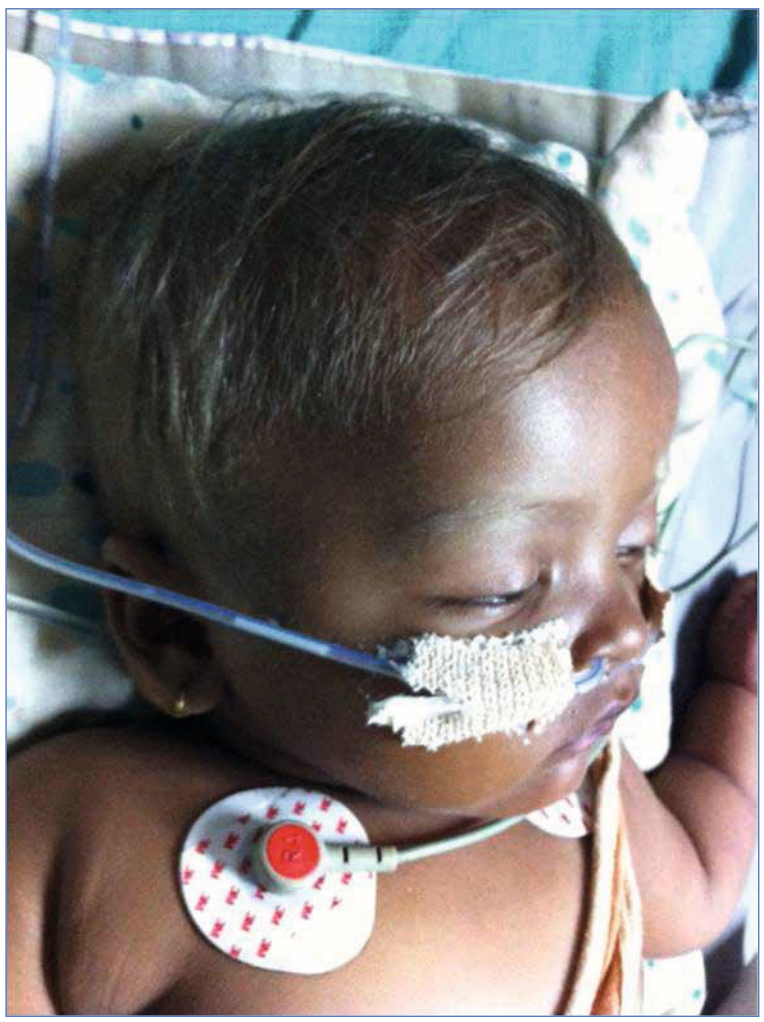
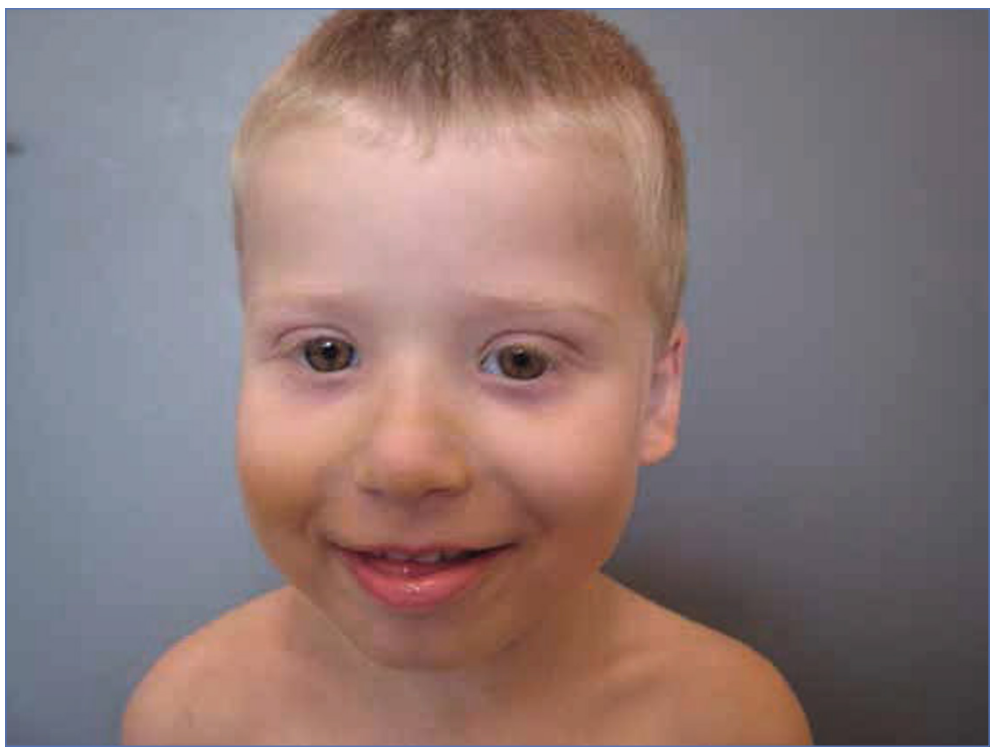
GRISCELLI-PRUNIERAS SYNDROME



Griscelli syndrome in an infant (coll. Arun Inamadar).



Pigmentary dilution of the skin and silvery hair in a boy with Griscelli syndrome.

Type 1

OMIM: #214450

GENETICS

Autosomal recessive inheritance with mutations in the MYO5A gene (15q21.2).

MOUSE MODEL

Myosin Va dilute.

PATHOPHYSIOLOGY

The MYO5A gene encodes a motor protein called myosin Va. One end of the myosin Va protein can bind the actin cytoskeleton, while the other can bind an organelle, in this case a melanosome. This linkage plays a key role in the transport of melanosomes within the melanocytes.
The expression of MYO5A in neurons explains the associated neurologic abnormalities in Griscelli syndrome type 1 (GS1). The MYO5A F-exon deletion only induces cutaneous defects.

Type 2

OMIM: #607624

GENETICS

Autosomal recessive inheritance with mutations in the RAB27A gene (15q21.3).

MOUSE MODEL

RAB27A.

PATHOPHYSIOLOGY

RAB27A encodes a small Ras-like GTPase (belonging to the Rab family) involved in the complex with myosin Va and melanophilin to transport the melanosomes within the melanocytes.
The expression of RAB27A in hematopoietic cells account for the immunodeficiency and hemophagocytic syndrome in GS2.

Type 3

OMIM: #609227

GENETICS

Autosomal recessive inheritance with mutations in the MLPH gene (2q37.3).

MOUSE MODEL

Leaden.

PATHOPHYSIOLOGY

The MLPH gene encodes a protein called melanophilin that forms a complex allowing the transport of the melanosomes on the actin fibers and the docking of the melanosomes at the extremities of the dendrite tips. Because expression of MLPH is limited to melanocytes, the associated phenotype consists of a pigmentary dilution and silvery hair.

EPIDEMIOLOGY

Griscelli syndrome is a rare. Most cases reported are from Turkish and Mediterranean populations.

CLINICAL DERMATOLOGICAL PRESENTATION

Pigmentary dilution of the skin.
Silvery gray hair.

EXTRACUTANEOUS SIGNS

Neurologic impairment in GS1 patients.
Immune abnormalities due to defective release of cytotoxic lysosomal contents from hematopoietic cells in GS2 patients. A hemophagocytic syndrome can also occur in GS2, with uncontrolled T-lymphocyte and macrophage activation leading to death ('activated phase').

HISTOPATHOLOGY

Hyperpigmented basal melanocytes with reduced pigmentation of the keratinocytes.
Clumped melanosomes in hair shafts.
Electron microscopy shows an aggregation of melanosomes in the perinuclear area of melanocytes with few melanosomes in the dendrite tips.

DIFFERENTIAL DIAGNOSIS

- Chediak–Higashi syndrome.
- Hermansky-Pudlak syndrome.
- OCA.

TREATMENT

There is currently no treatment for GS1.
Hematopoietic stem cell transplantation is the treatment for GS2. Antivirals and antibiotics are also used.

KEY REFERENCES

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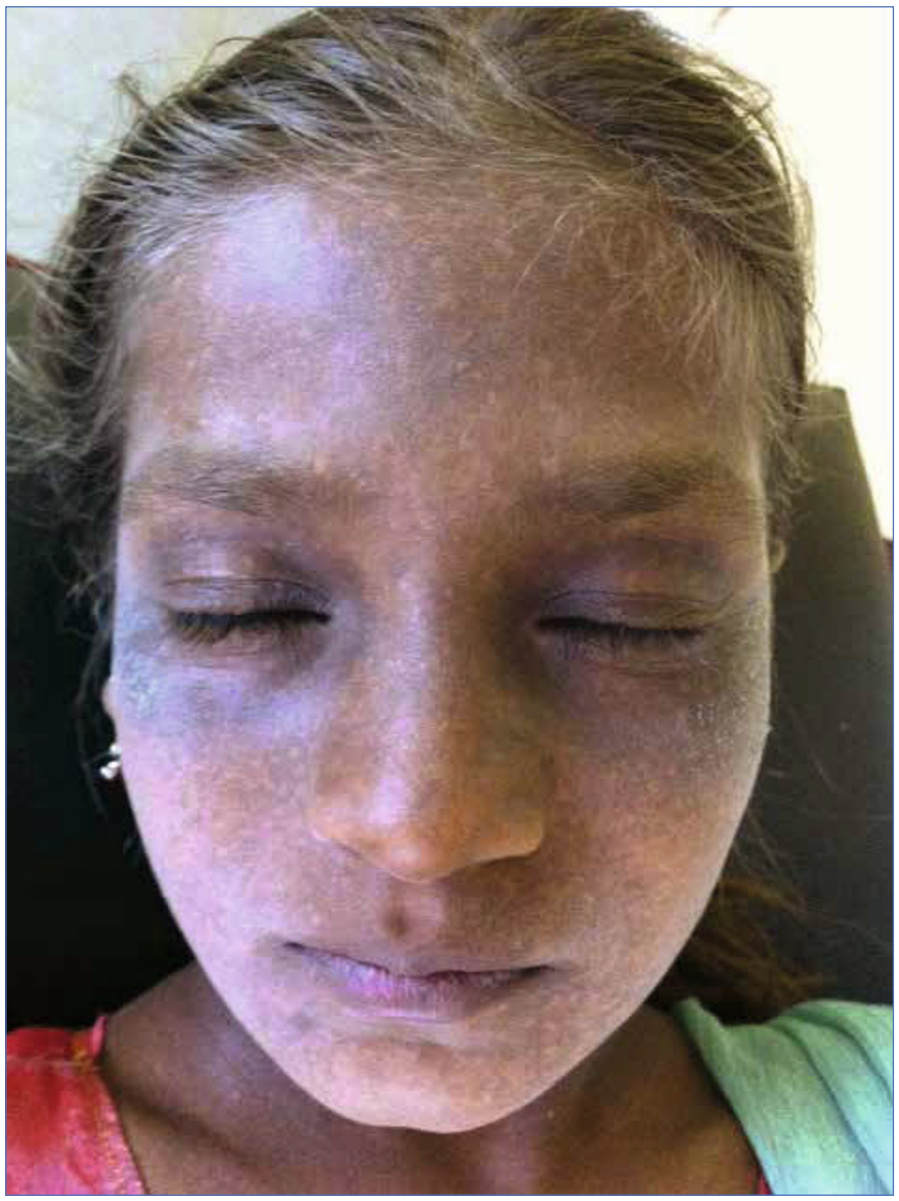
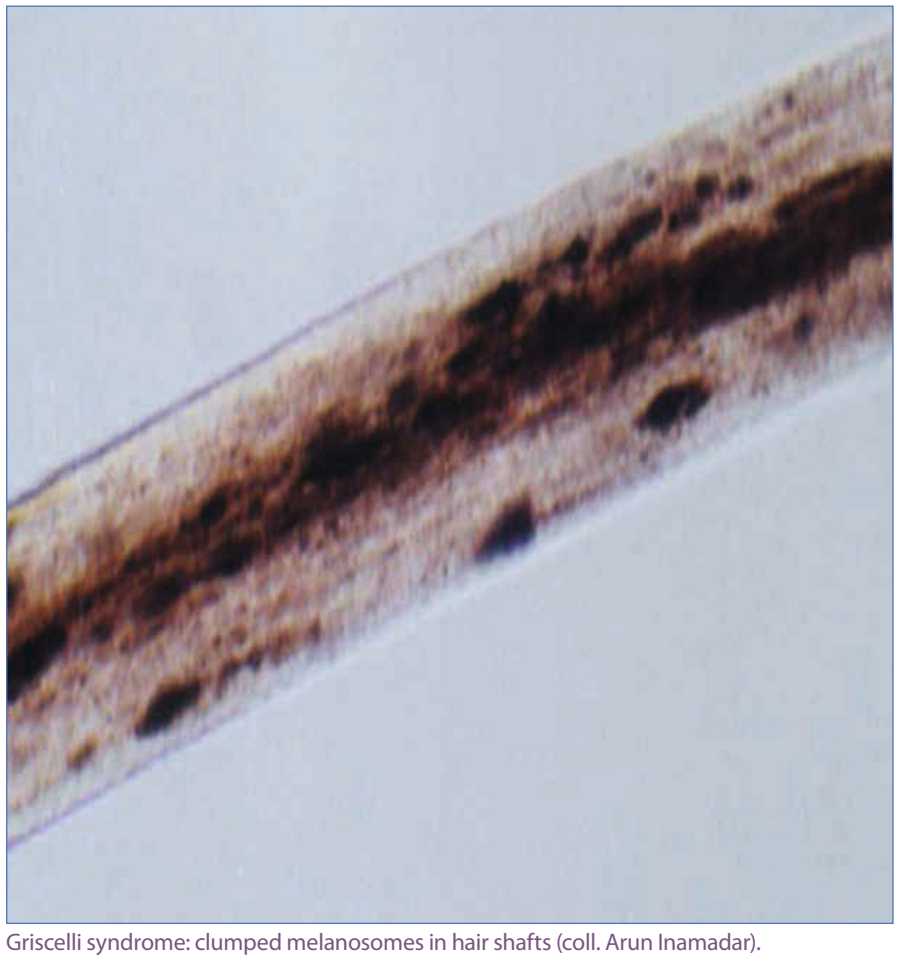
- Menasche G, Pastural E, Feldmann J, et al. Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. Nature Genet. 2000;25:173-6.
- Ménasché G, Ho CH, Sanal O, Feldmann J, Tezcan I, Ersoy F, Houdusse A, Fischer A, de Saint Basile G. Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F-exon deletion (GS1). J Clin Invest. 2003;112:450-6. Erratum in: J Clin Invest. 2005;115:1100.

GRISCELLI-PRUNIERAS SYNDROME



Griscelli syndrome: pigmentary dilution of the skin and silvery hair (coll. Arun Inamadar).



Griscelli syndrome: clumped melanosomes in hair shafts (coll. Arun Inamadar).

HERMANSKY-PUDLAK SYNDROME

Type 1

OMIM: #203300
GENETICS
Autosomal recessive inheritance with mutations in the HPS1 gene (10q24.2).

MOUSE MODEl
Pale ear.

EPIDEMIOLOGY
Hermansky-Pudlak syndrome (HPS) type 1 is the most common form of HPS.
Most cases have been described in Puerto Rico and the Arecibo region. HPS has a frequency of about 1 in 1,800 in Puerto Rico giving a carrier frequency estimated to be 1 in 21.

PATHOPHYSIOLOGY
The HPS1 gene product is a component of a complex called biogenesis of lysosome-related organelles complex (BLOC)-3.
This BLOC-3 complex is involved in the formation of lysosome-related organelles, including melanosomes, by a mechanism distinct from that operated by the adaptor protein 3 (AP-3) complex.

Type 2

OMIM: #608233
GENETICS
Autosomal recessive inheritance with mutations in the AP3B1 gene (5q14.1).

MOUSE MODEL
Pearl.

EPIDEMIOLOGY
Very rare condition.

PATHOPHYSIOLOGY
AP3B1 encodes the β3A subunit of the AP-3 complex; the latter is involved in protein sorting to lysosomes and lysosome-related organelles.
CD1b binds to the AP-3 complex, and defects in CD1b-associated antigen presentation may account for the recurrent bacterial infections observed in patients with HPS type 2.

Type 3

OMIM: #614072
GENETICS
Autosomal recessive inheritance with mutations in the HPS3 gene (3q24).

MOUSE MODEL
Cocoa.

EPIDEMIOLOGY
This subtype, along with HPS type 1 is the most common forms seen in Puerto Ricans.

PATHOPHYSIOLOGY
The HPS3 gene encodes a cytoplasmic protein which is a component of BLOC-2.
As with BLOC-3, BLOC-2 is involved in the biogenesis of lysosome-related organelles via a mechanism distinct from that of the AP-3 complex.

Type 4

OMIM: #614073
GENETICS
Autosomal recessive inheritance with mutations in the HPS4 gene (22q11.2–12.2).

MOUSE MODEL
Light ear.

EPIDEMIOLOGY
Very rare condition.

PATHOPHYSIOLOGY
HPS4 is a component of BLOC-3.

Type 5

OMIM: #614074
GENETICS
Autosomal recessive inheritance with mutations in the HPS5 gene (11p15–p13).

MOUSE MODEL
Ruby eye 2.

EPIDEMIOLOGY
Very rare condition.

PATHOPHYSIOLOGY
HSP5 encodes a cytosolic protein which is a component of the BLOC-2 complex.
As with BLOC-3, BLOC-2 is involved in the biogenesis of lysosome-related organelles via a mechanism distinct from that of the AP-3 complex.

Type 6

OMIM: #614075
GENETICS
Autosomal recessive inheritance with mutations in the HPS6 gene (10q24.32).

MOUSE MODEL
Ruby eye.

EPIDEMIOLOGY
Very rare condition.

PATHOPHYSIOLOGY
HSP6 encodes a cytosolic protein which is a component of the BLOC-2 complex.

Type 7

OMIM: #614076
GENETICS
Autosomal recessive inheritance with mutations in the DTNBP1 gene (6p22.3).

MOUSE MODEL
Sandy.

EPIDEMIOLOGY
Very rare condition.

PATHOPHYSIOLOGY
DTNBP1 encodes dysbindin, a protein that binds to α- and β-dystrobrevins, components of the dystrophin-associated protein complex in both muscle and non-muscle cells. However, dysbindin is also a component of BLOC-1, explaining why this protein is important for normal platelet dense granule and melanosome biogenesis.

Type 8

OMIM: #614077
GENETICS
Autosomal recessive inheritance with mutations in the BLOC1S3 gene (19q13).

MOUSE MODEL
Reduced pigmentation (rp).

EPIDEMIOLOGY
Very rare condition.

PATHOPHYSIOLOGY
BLOC1S3 gene encodes for a protein involved in the BLOC-1 complex.

Type 9

OMIM: #614171
GENETICS
Autosomal recessive inheritance with mutations in the PLDN gene (15q21).

MOUSE MODEL
Pallid.

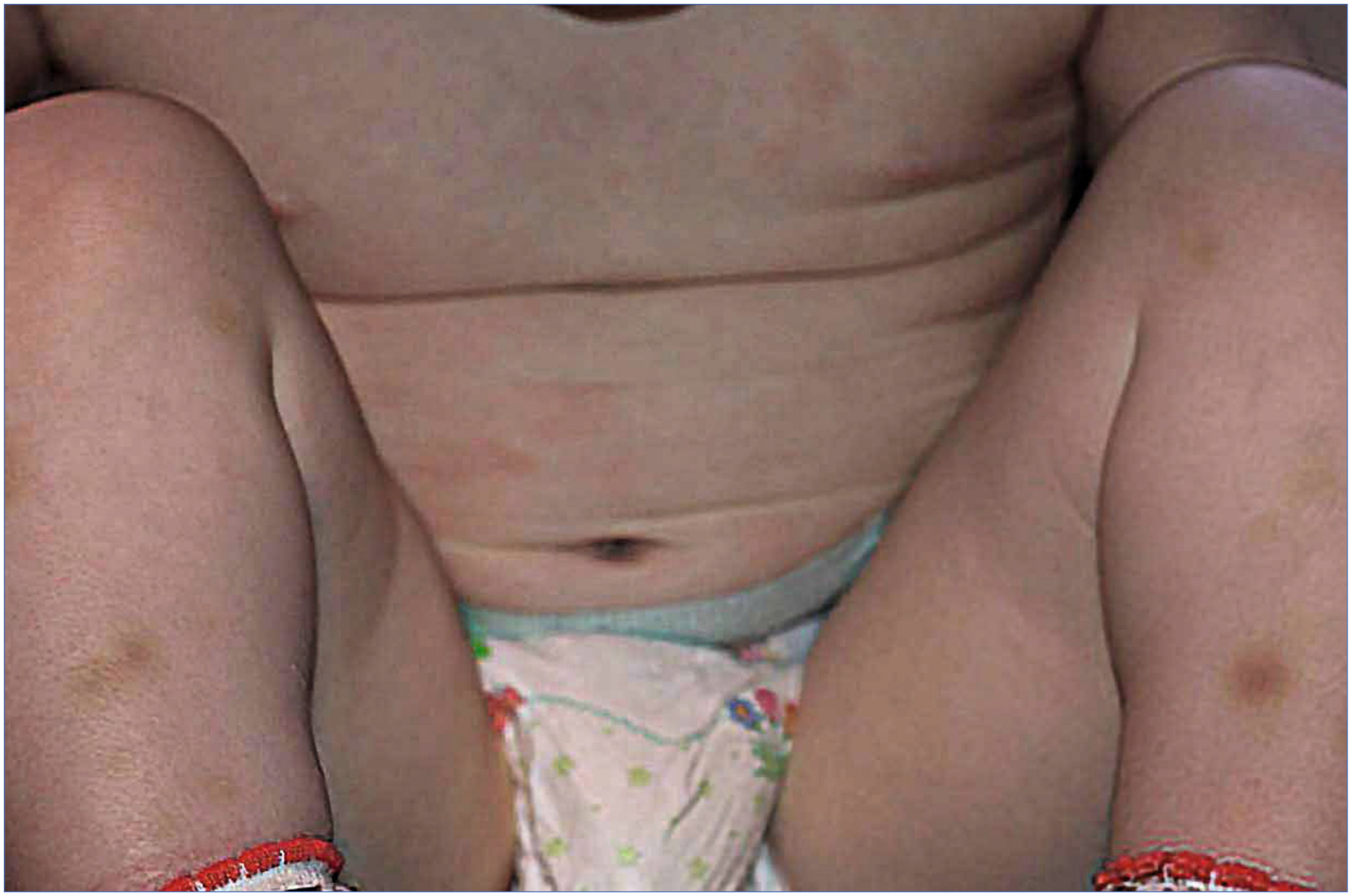
EPIDEMIOLOGY
Very rare condition (1 case described so far).

PATHOPHYSIOLOGY
The PLDN gene encodes the pallidin protein, which is involved in vesicle docking and fusion. Pallidin is a component of BLOC-1.

CLINICAL DERMATOLOGICAL PRESENTATION
Pigmentary dilution of the skin, hair and eyes (as to be compared with unaffected first-degree relatives).
The degree of the pigmentary dilution can vary, depending upon the underlying mutations and ethnic origin.
With age, an increase in pigmentation is usually seen, but patients still have difficulty tanning.
Ocular manifestations of albinism, such as nystagmus and reduced visual acuity, are also present.
Easily bruised.

EXTRACUTANEOUS SIGNS
They are linked to the ceroid lipofuscin accumulation within lysosomes.
Bleeding tendency (eg, with tooth extraction or childbirth). The bleeding time and PFA-100 test are prolonged due to platelet dysfunction.
Interstitial pulmonary fibrosis.
Granulomatous colitis.
Less often, renal failure and cardiomyopathy develop, usually during adulthood.
HPS type 2 differs from the other forms of HPS in that its phenotype includes immunodeficiency (increased susceptibility to infections due to congenital neutropenia).
No immunodeficiency, granulomatous colitis, or pulmonary fibrosis has been observed so far in the child with HPS type 9.

HERMANSKY-PUDLAK SYNDROME



Pigmentary dilution of the skin (as compared to first-degree relatives) and multiples bruises in a child with Hermansky-Pudlak syndrome (coll. Franck Boralevi).

HISTOPATHOLOGY

Ceroid deposits, derived from the degradation of lipids and glycoproteins, are within lysosomes in affected internal organs.
Electron microscopy shows the presence of hair bulb tyrosinase as well as stage I to III (rarely stage IV) melanosomes and macromelanosomes.

DIFFERENTIAL DIAGNOSIS

- Griscelli syndrome.
- Chediak–Higashi syndrome.
- OCA.

TREATMENT

Genetic counseling.
The antifibrotic agent pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone), appears to slow the progression of pulmonary fibrosis in HPS patients who have significant residual lung function, but does not stop the process entirely.

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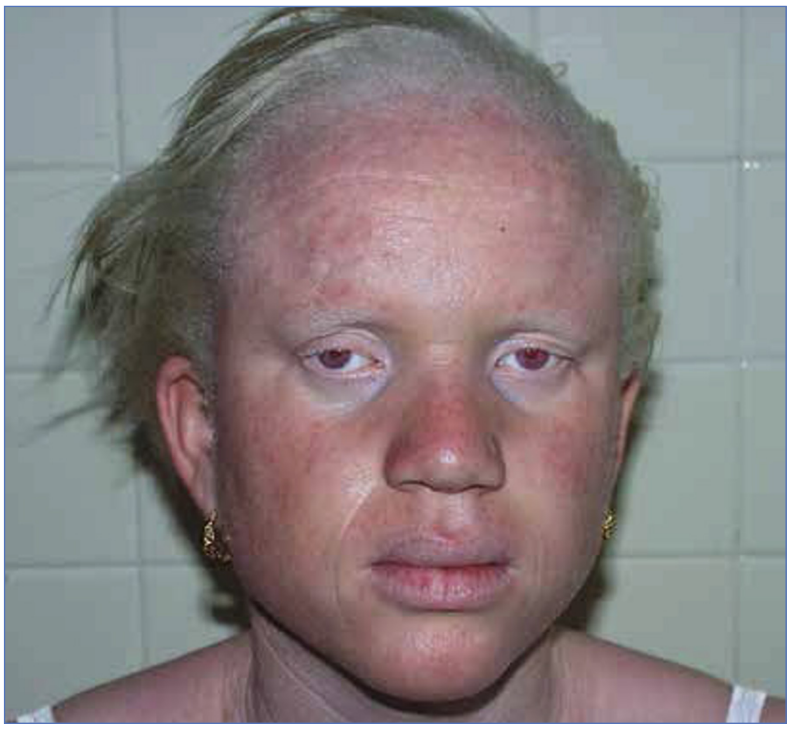
OCULOCUTANEOUS ALBINISMS

Jean-Philippe Lacour

Young Caucasian infant with oculocutaneous albinism type 1.



Oculocutaneous albinism type 1 in a negroid woman.

Oculocutaneous albinism (OCA) is a group of genetic disorders of melanin synthesis characterized by a generalized reduction in pigmentation of hair, skin and eyes, associated with variable ocular anomalies including nystagmus, reduced visual acuity and photophobia. Variants include OCA1A (the most severe form), OCA1B, OCA1-minimal pigment (OCA1-MP), OCA1-temperature sensitive (OCA1-TS), OCA2, OCA3 (or Rufus albinism), OCA4, OCA5, OCA6 and OCA7.

OMIM: OCA1, #203100; OCA2, #203200; OCA3, #203290; OCA4, #606574; OCA5, #615312; OCA6, #113750; OCA7, #615179

GENETICS

Autosomal recessive inheritance with mutations in various genes that control the synthesis of melanin by melanocytes, depending on the type of albinism.

- OCA1-MP and OCA1-TS are caused by mutations in the TYR gene (11q14.3).
- OCA2 is due to mutations in the OCA2 gene (15q12-q13).
- OCA3 is due to mutations in the TYRP1 gene (9p23).
- OCA4 is caused by mutations in the SLC45A2 gene (5p13.2).
- OCA5 is caused by mutations in a gene, located on chromosome 4q24.
- OCA6 is due to mutations in the SLC24A5 gene (15q21.1).
- OCA7 is due to a mutation in C10orf11 gene (10q22.3).

MOUSE MODEL (IF ANY)

OCA1A: Tyrc-2J/c-2J mouse.
OCA1B Tyrc-h/c-h mouse (Himalayan mouse).
OCA2: several 'pink-eyed dilution' strains in mice, including 'pink-eyed unstable' (Oca2p-un).
OCA4: uw/uw mouse (underwhite).

EPIDEMIOLOGY

The prevalence of all forms of albinism varies considerably worldwide and has been estimated at approximately 1 in 17,000. OCA1 has a prevalence of approximately 1 per 40,000. OCA2 is the most common type of albinism, particularly among people of African ancestry. Other forms are much rarer.

PATHOPHYSIOLOGY

- OCA1 is caused by mutations in the tyrosinase gene. Mutations that completely abolish tyrosinase activity result in OCA1A, while mutations that reduce enzyme activity result in OCA1B, allowing some accumulation of melanin pigment over time.
- OCA2 is caused by mutations in the OCA2 gene (formerly P-gene) encoding the melanosomal OCA2 protein that possibly regulates melanosomal pH. It is essential for normal biogenesis of melanosomes and for normal processing and transport of melanosomal proteins such as TYR and TYRP1.
- OCA3 is caused by mutations in TYRP1 encodes an enzyme in the melanin biosynthesis pathway that catalyzes the oxidation of 5,6-dihydroxyindole-2-carboxylic acid (DHICA) monomers into melanin. Its function is to stabilize tyrosinase, and mutations in this gene cause a delayed maturation and an early degradation of tyrosinase.
- OCA4 is caused by mutations in the gene that encodes membrane associated transport protein (MATP), which is responsible for melanosome function and protein transport.

CLINICAL DERMATOLOGICAL PRESENTATION

The degree of skin and hair hypopigmentation varies with the type of OCA.

- OCA1A: white hair, eyelashes and eyebrows. Skin never tans. Amelanotic nevi may be present. The symptoms do not vary with age or race.
- OCA1B: hair and skin may develop some pigment with time.
- OCA1-TS: depigmented body hairs, pigmented hairs on hands and feet due to lower temperatures.
- OCA2: various amount of cutaneous pigment. Newborns nearly always have pigmented hair. Nevi and ephelids are common.
- OCA3 (Rufous or red OCA): red hair and reddish brown skin in African individuals.
- OCA4: cannot be distinguished from OCA2 based on clinical findings.
- OCA5: white skin, golden hair.
- OCA6: white skin, light hair at birth that darkens with age.
- OCA7: skin from light blond to dark brown, lighter than relatives.

Photosensitivity: most people with severe forms of OCA do not tan and easily get sunburned.
Skin cancers may occur, particularly in OCA1A.

EXTRACUTANEOUS SIGNS

Ocular manifestations include various degrees of congenital nystagmus, iris hypopigmentation and translucency, reduced pigmentation of the retinal pigment epithelium, foveal hypo-plasia, reduced visual acuity (20/60 to 20/400) and refractive errors, color vision impairment and photophobia. Misrouting of the optic nerves is a characteristic finding, resulting in strabismus and reduced stereoscopic vision.

HISTOPATHOLOGY

In OCA1 and OCA2 melanocytes have a normal structure and are normally present, but the use of Fontant-Masson silver staining does not demonstrate melanin. By electron microscopy melanosomes have a complete absence of melanin in OCA1 whereas there are some melanosomes with melanin in OCA2. Normal structure of melanocytes is demonstrated in both types.

DIFFERENTIAL DIAGNOSIS

- Ocular Albinism (OA): hypopigmentation limited to the eyes. In patients with light complexion, some difficulty in the differential diagnosis with OA is not uncommon.
- Hermansky-Pudlak syndrome.
- Chediak-Higashi syndrome (CHS).
- Griscelli syndrome.
- Waardenburg syndrome type II (WS2).

TREATMENT

Skin:
Photoprotection: avoid sun exposure, use sunscreens of high SPF, wear hats and sun-protective clothing.
Management of eye problems:
Glasses to correct impairment of vision, sunglasses for phototophobia, treatment of nystagmus. Special help and material for children at school.

KEY REFERENCES

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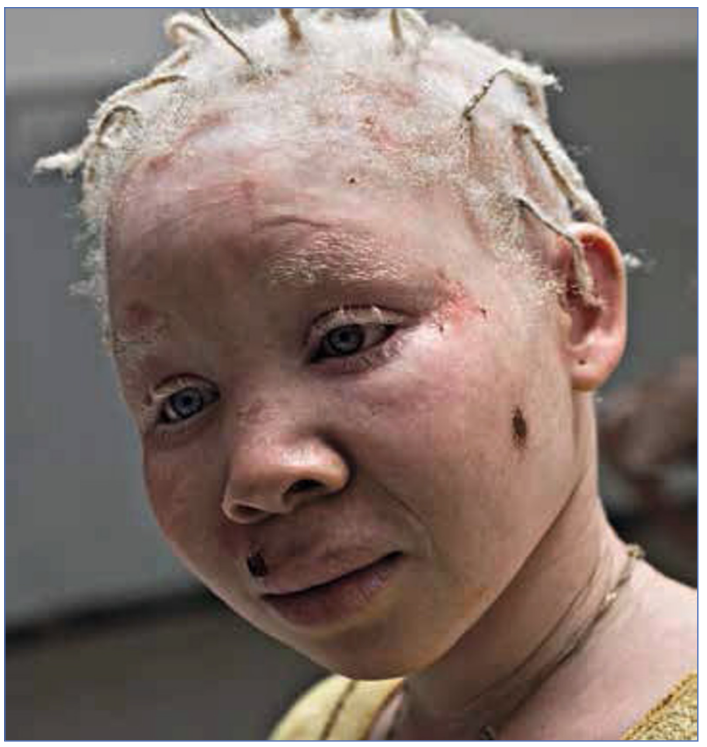
- Montoliu L, Grønskov K, Wei AH, Martínez-García M, Fernández A, Arveiler B, Morice-Picard F, Riazuddin S, Suzuki T, Ahmed ZM, Rosenberg T, Li W. Increasing the complexity: new genes and new types of albinism. Pigment Cell Melanoma Res. 2014;27:11-8.

OCULOCUTANEOUS ALBINISMS

Ocular albinism. The presence of a nystagmus allowed the diagnosis (coll. Ana Yturralde).

Young woman with oculocutaneous albinism type 2. Note the presence of numerous nevi and ephelids (coll. Ana Yturralde).

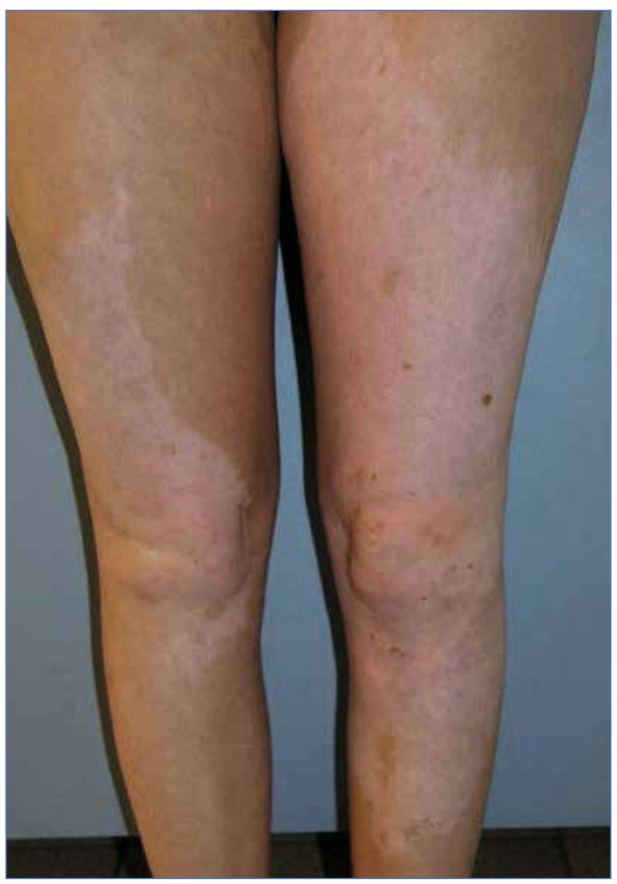
Young boy with oculocutaneous albinism type 2 sitting with his mother (coll. Ana Yturralde). Pictures kindly provided by Ana Yturralde (www.anayturralde.com). Pictures included in the book: Albinismo, una condicion genetica, dos realidades: Espagna y Senegal, published by ALBA (2009), the Spanish Association in support of people with albinism (www.albinismo.es). This book has been translated to French by Genespoir (2012), the French Organization for albinism (www.genespoir.org).



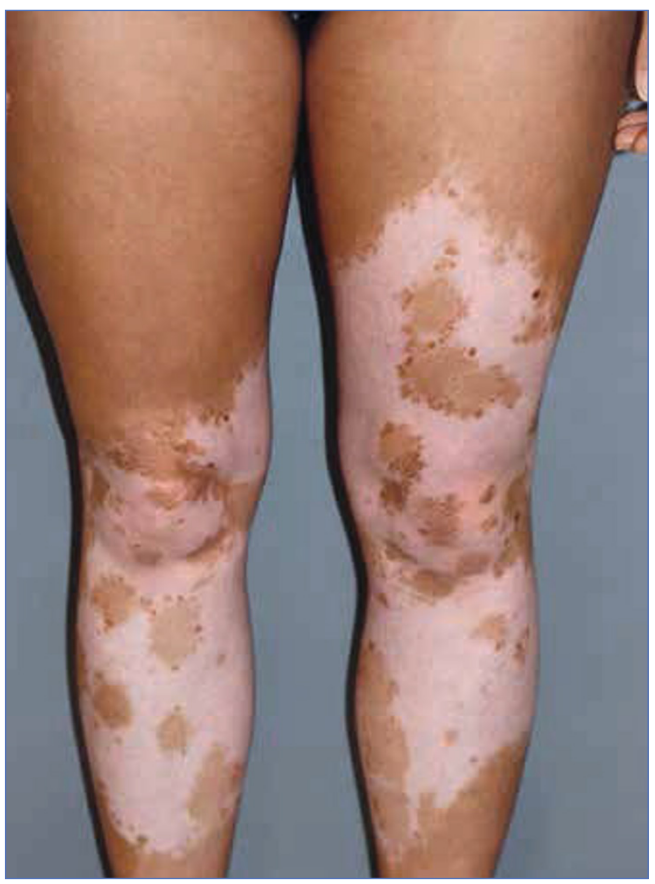
Young girl with oculocutaneous albinism type 1. Note the actinic damages on the skin. (coll. Ana Yturralde).

PIEBALDISM

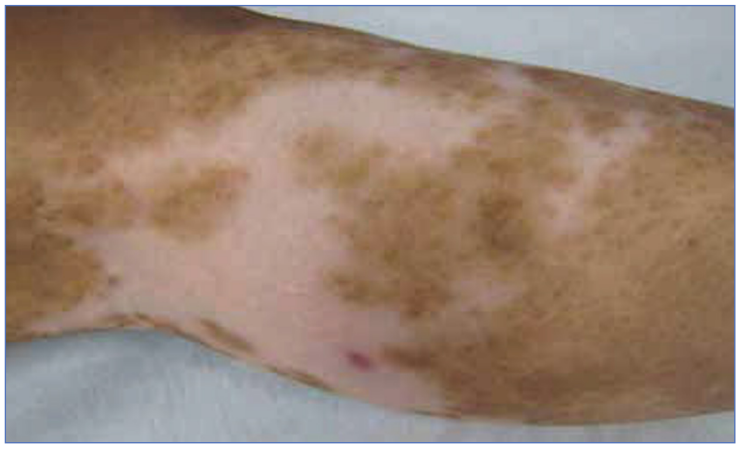
Nanja van Geel



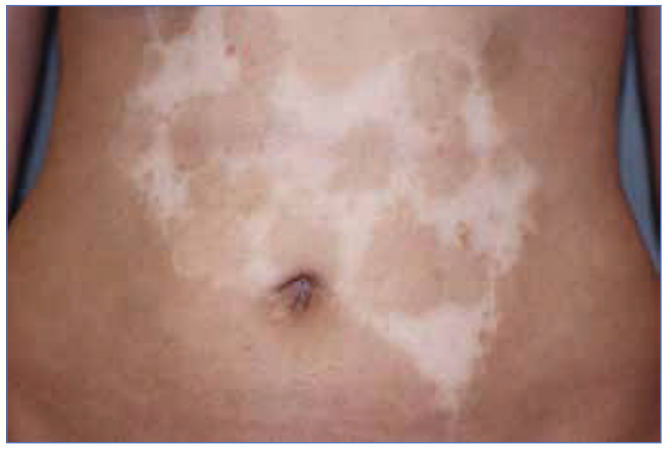
Large areas of depigmentation with few hyperpigmented macules (coll. Nanja van Geel).



Symmetrically distributed depigmentations of the legs associated with hyperpigmented macules.



Close-up of a lesion of the leg. note the characteristic association of completely depigmented patches with normal or hyperpigmented macules.



Abdominal lesion in a patient with piebaldism.

OMIM: #172800

GENETICS

Autosomal dominant inheritance with mutation in the c-kit proto-oncogene, mapped to the proximal long arm of chromosome 4 (4q12) or from deletions in the SLUG gene (SNAI2), which is a zinc-finger neural crest transcription factor.

MOUSE MODEL

Piebald mouse.

EPIDEMIOLOGY

Rare autosomal dominant disorder.
Less than 1:20,000; cases have been reported in all races.
Males and females are equally affected.

PATHOPHYSIOLOGY

Underlying defect of the tyrosine kinase transmembrane receptor on melanocytes, leading to an impaired embryonic migration and survival of melanocytes in the skin.

CLINICAL DERMATOLOGICAL PRESENTATION

Congenital, extensive, symmetrically distributed depigmentations mainly on forehead (often triangular in shape), front of thorax and extremities often associated with presence of hyperpigmented macules within the areas of depigmentation.
The extent of the lesions is variable, ranging from only a midfrontal poliosis or white forelock (present in 80-90% of the patients) and minimal areas of depigmentation to extensive depigmentation over the entire body.

EXTRACUTANEOUS SIGNS

If associated with extracutaneous signs consider Waardenburg's syndrome (see differential diagnosis).

HISTOPATHOLOGY

Histology from depigmented area reveals decreased number or total absence of melanocytes and melanin.

DIFFERENTIAL DIAGNOSIS

- Waardenburg syndrome (similar clinical presentation, but is associated with heterochromia iridis, dystopia canthorum, congenital deafness and occasionally a congenital megacolon [Hirschsprung's disease]).
- Vitiligo.

TREATMENT

Camouflage or surgical grafting. Good results have been reported with autologous non-cultured epidermal cell transplantation.

KEY REFERENCES

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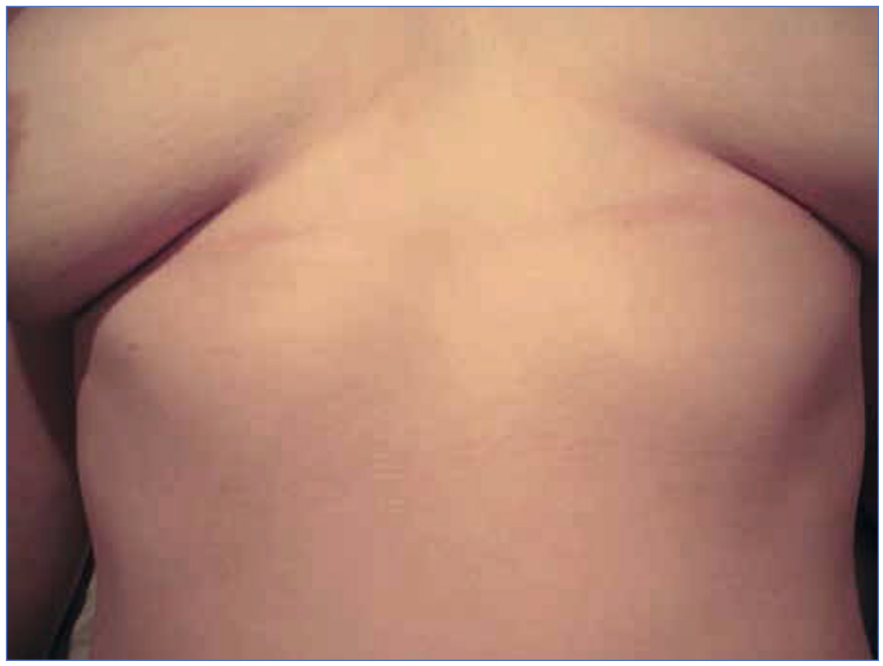
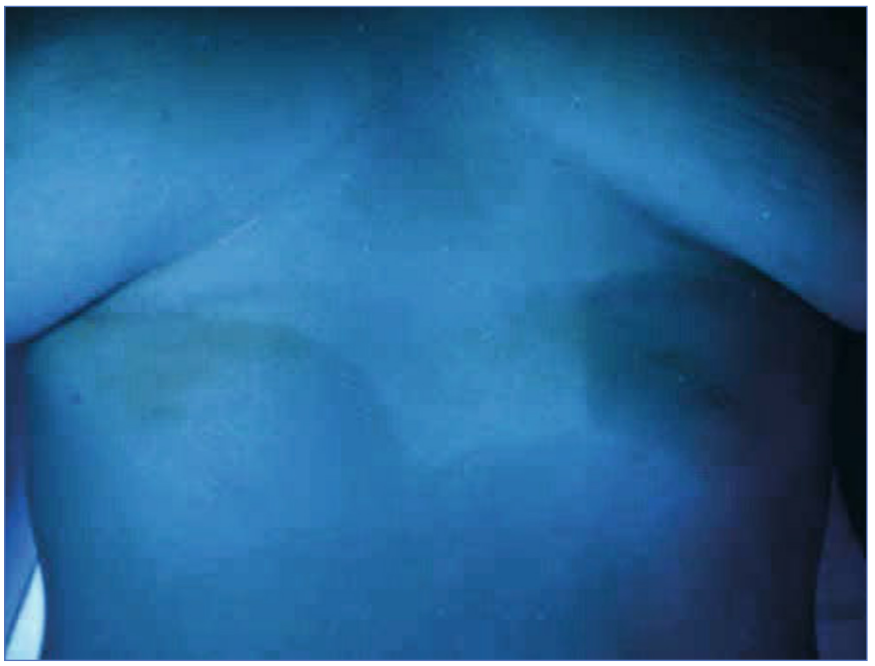
PIEBALDISM

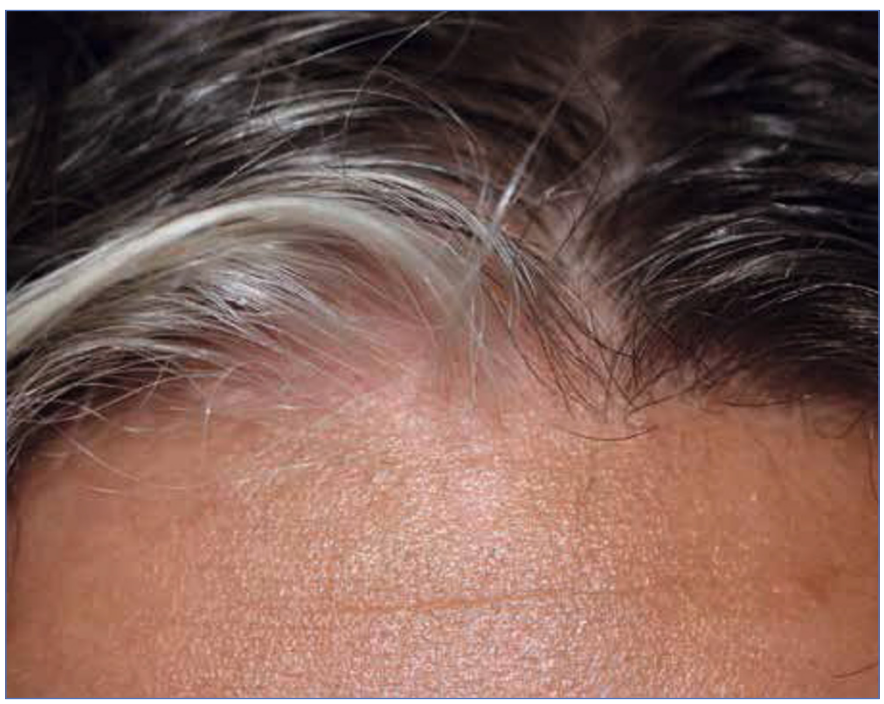
Nanja van Geel



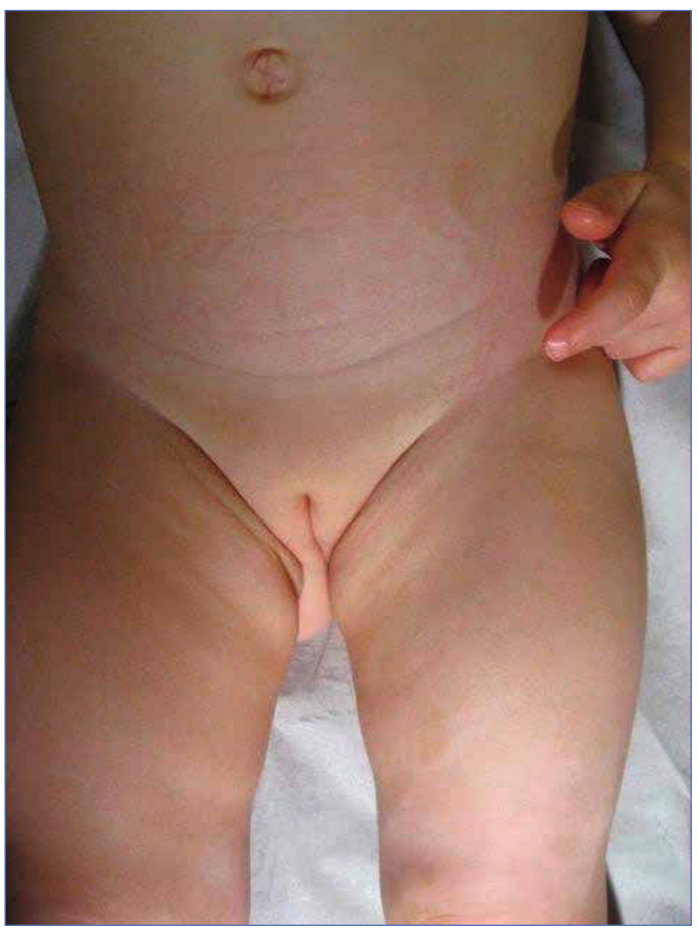
A. The hypopigmented lesions can be sometimes difficult to see in fair skin patient. This woman presented with depigmented patches on the legs associated with this lesion on the anterior trunk.



B. The hypopigmentation appears clearly under Woods' lamp examination.



Typical white forelock.



Congenital achromic patches in a newborn with piebaldism.

WAARDENBURG SYNDROME

Waardenburg and Tietz syndromes (WS) are rare autosomal dominant or autosomal recessive disorders affecting genes involved in the development of melanocytes during the embryogenesis.

Waardenburg syndrome	OMIM	Mouse model	Mode of inheritance	Gene mutated (chromosome)	Protein
WS1	193500	Sploch	AD	PAX3 (2q36.1)	PAX3 transcription factor
WS2 A	193510	Microphthalmia	AD	MITF (3p14.1-p12.3)	MITF transcription factor
B	600193	None	AD	? (1p21-p13.3)	
C	606662	None	AD	? (8p23)	Zinc finger transcription factor SRY-box containing gene 10
D	608890	SLUG-null mice	AD	SNAI2 or SLUG (8q11)	
E	611584	Dominant megacolon	AD	SOX10 (22q13)	
WS3	148820	Sploch	AD	PAX3 (2q36.1)	PAX3 transcription factor
WS4 A	277580	Piebald spotting		EDNRB (13q22)	Endothelin B receptor
B	613265	Lethal spotting		EDN3 (20q13.)	Endothelin-B
C	613266	Dominant megacolon	AD and AR	SOX10 (22q13)	SRY-box containing gene 10
Tietz syndrome	103500		AD	SOX10 (22q13)	SRY-box containing gene 10

AD: autosomal dominant ; AR: autosomal recessive.

EPIDEMIOLOGY

The incidence of WS in the Netherlands has been estimated at 1 in 212,000. In the US, deafness in the setting of WS afflicts 2 in 100,000.
Cases have been reported in all races and from all regions of the world.
Men and women are equally affected.

PATHOPHYSIOLOGY

The genes involved in WS encode for protein that play a key role in melanocyte development. Depending on the gene involved other neural crest-derived cells may be affected explaining the phenotypes that are observed.

CLINICAL DERMATOLOGICAL PRESENTATION

Pigmentary abnormalities of the hair:
- White forelock. In most cases, the forelocks are white, but patches of red, brown or black hair have been observed.
- Additional areas of poliosis can be associated.
- Premature graying.

Depigmented patches (similar to those observed in piebaldism).
Pigmentary changes of the iris, such as heterochromia irides and brilliant blue eyes.

EXTRACUTANEOUS SIGNS

Congenital sensorineural hearing loss (more common in WS2).
Dystopia canthorum (not observed in WS2).
Upper limb abnormalities (e.g. hypoplasia, syndactyly) (in WS3).
Association with Hirschsprung disease (in WS4).
Tietz syndrome:
The clinical phenotype of this rare syndrome is significantly different from WS2, despite being allelic.
Generalized hypomelanosis of the skin, hypoplasia of the eyebrows, light blond hair, and blue eyes (with photophobia and nystagmus) and deaf-mutism.

HISTOPATHOLOGY

Absence or minimal number of melanocytes in depigmented areas.

DIFFERENTIAL DIAGNOSIS

- Piebaldism.
- Vitiligo.

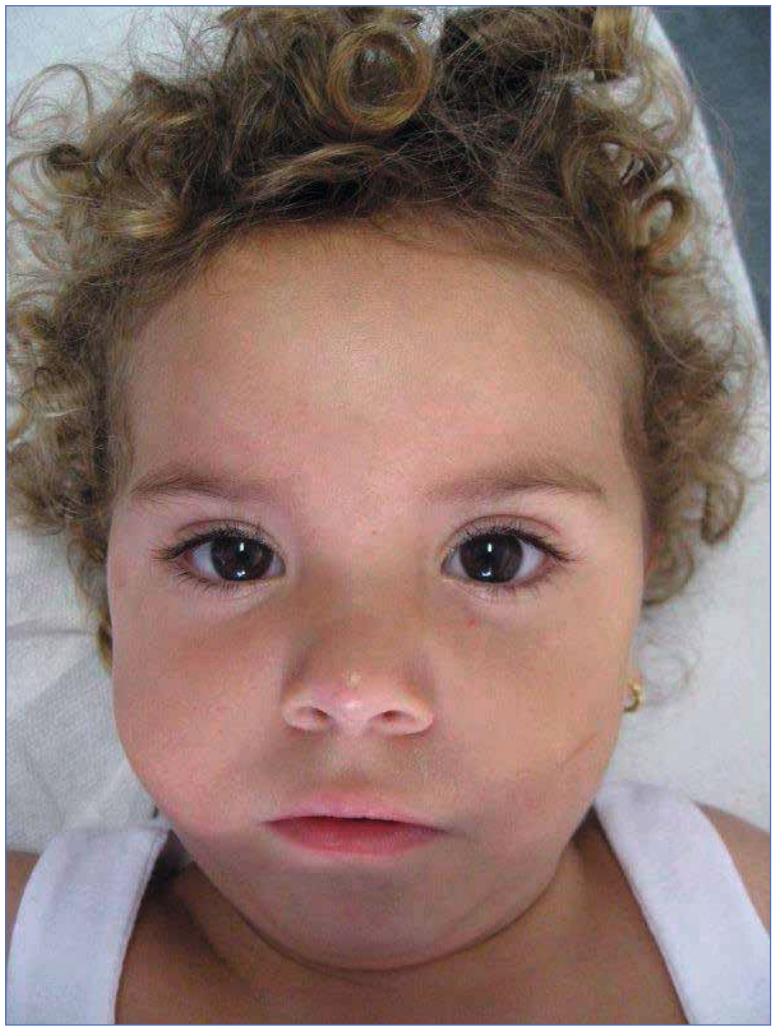
TREATMENT

Genetic counseling.
Early diagnosis allows appropriate management of the deafness.

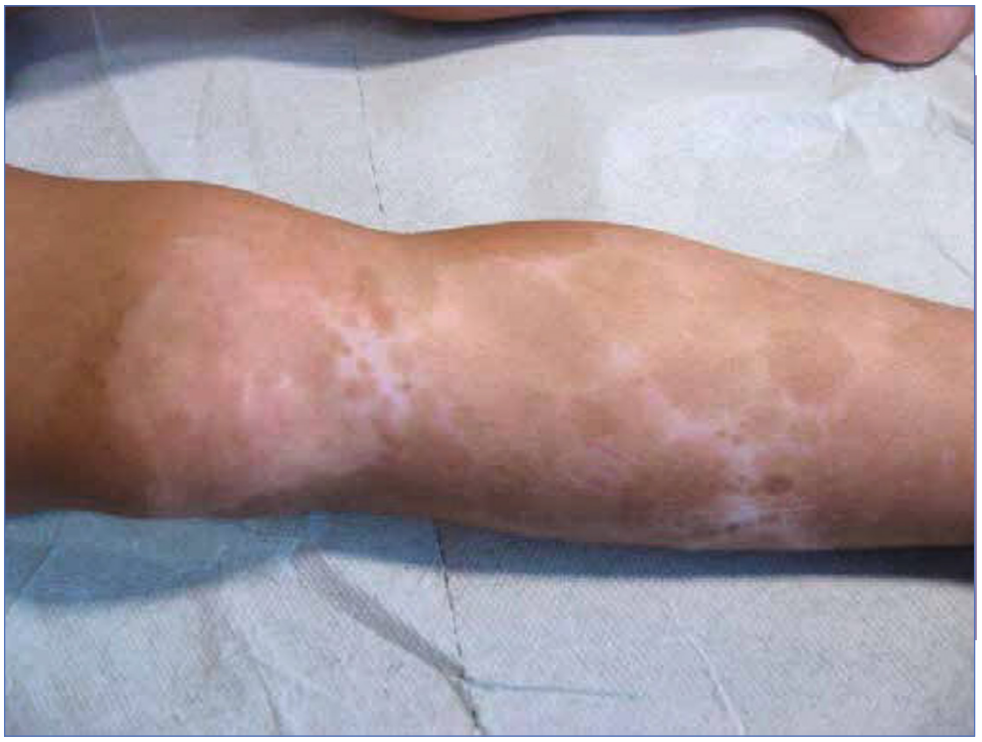
KEY REFERENCES

- Passeron T, Mantoux F, Ortonne JP. Genetic disorders of pigmentation. Clin Dermatol. 2005;23:56-67.
- Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, Bondurand N. Review and update of mutations causing Waardenburg syndrome. Hum Mutat. 2010;31:391-406.

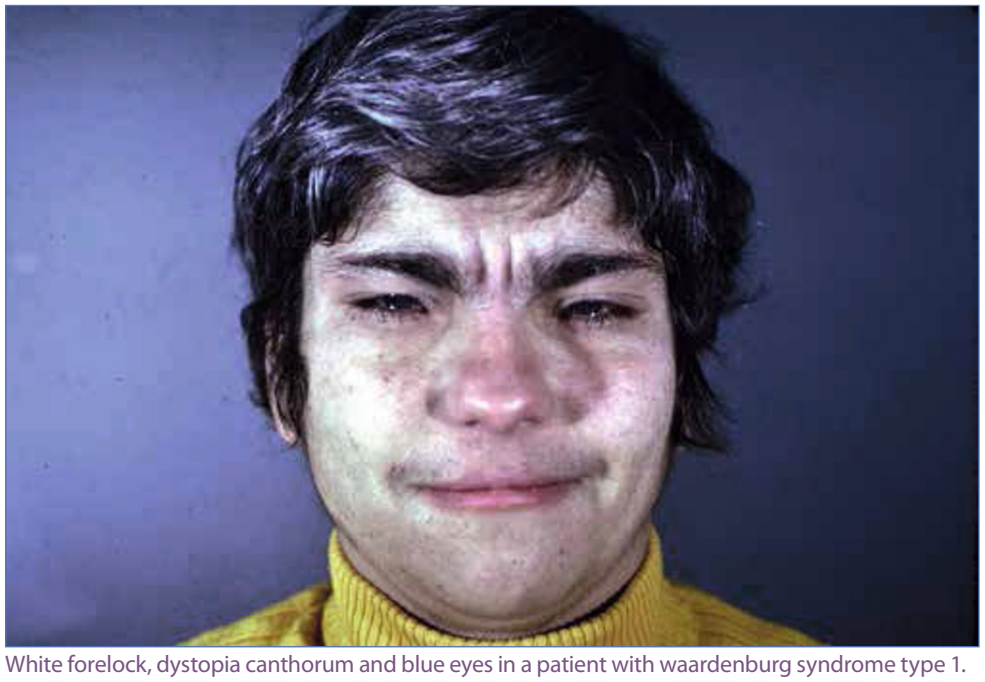
WAARDENBURG SYNDROME



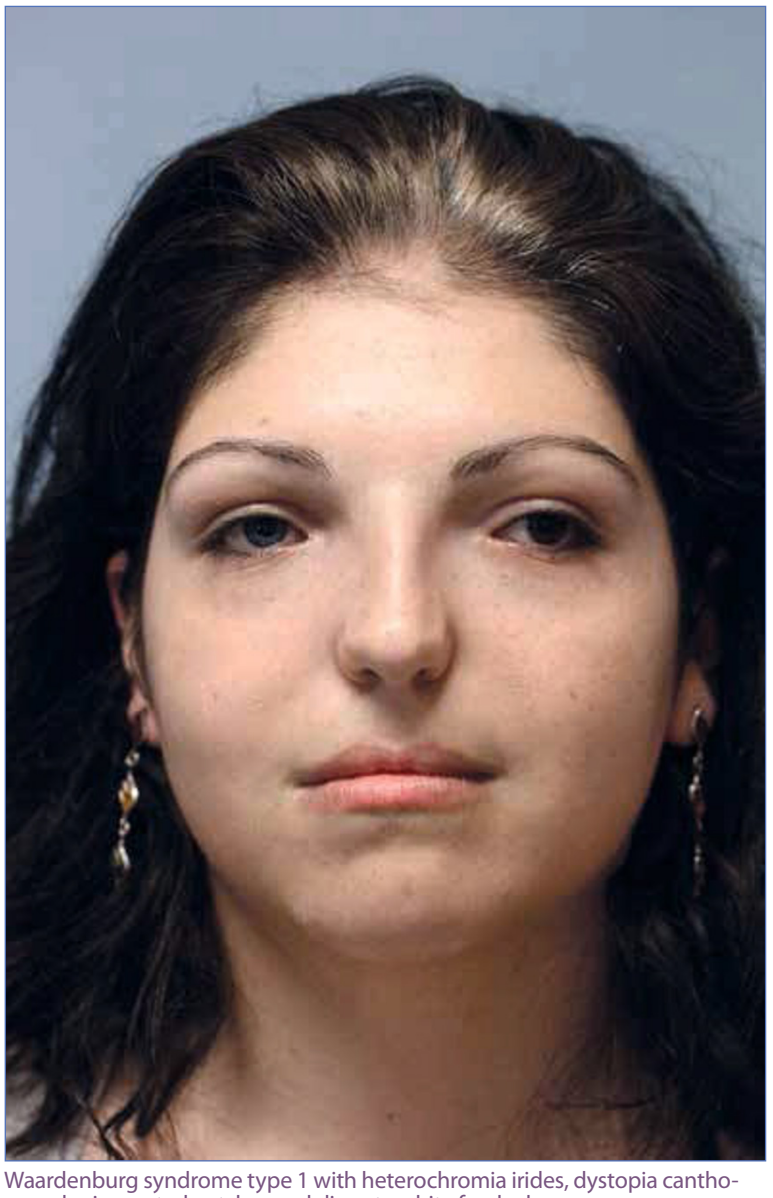
Dystopia canthorum in a young girl with Waardenburg syndrome type 1. The white forelock is absent in this patient.



Depigmented patches on the leg on the same woman with Waardenburg syndrome type 1. The pattern of depigmentation is similar to the one observed in piebaldism.



White forelock, dystopia canthorum and blue eyes in a patient with waardenburg syndrome type 1.



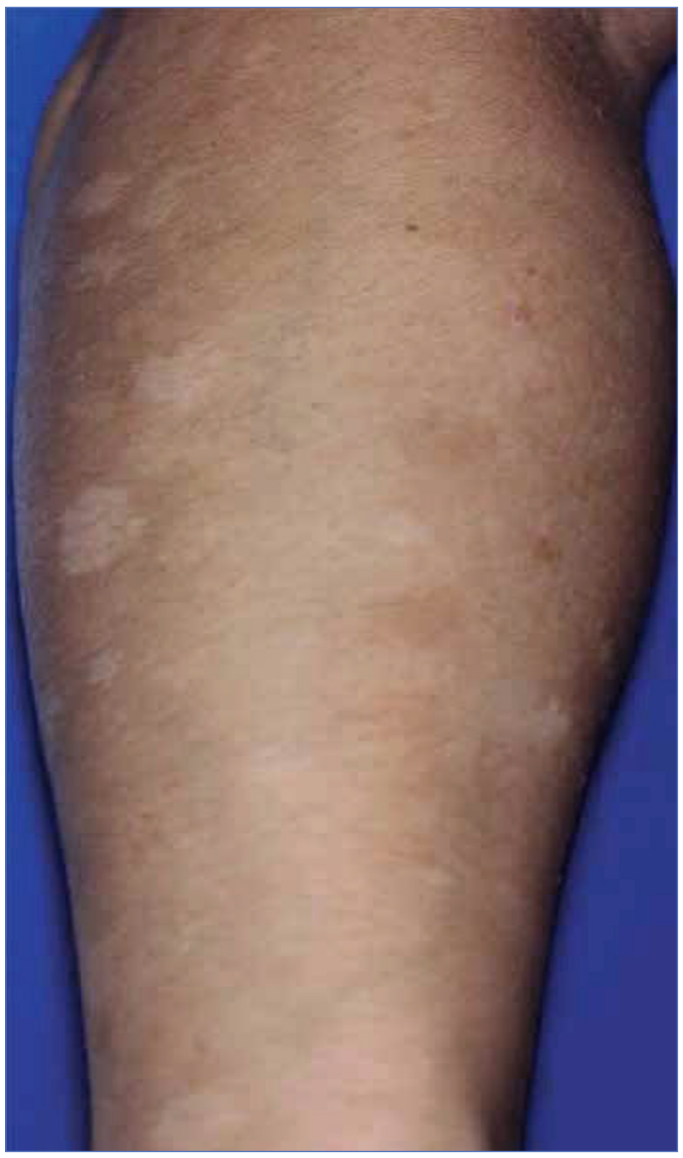
Waardenburg syndrome type 1 with heterochromia irides, dystopia canthorum, depigmented patches and discrete white forelock.

GENETIC HYPOMELANOSIS

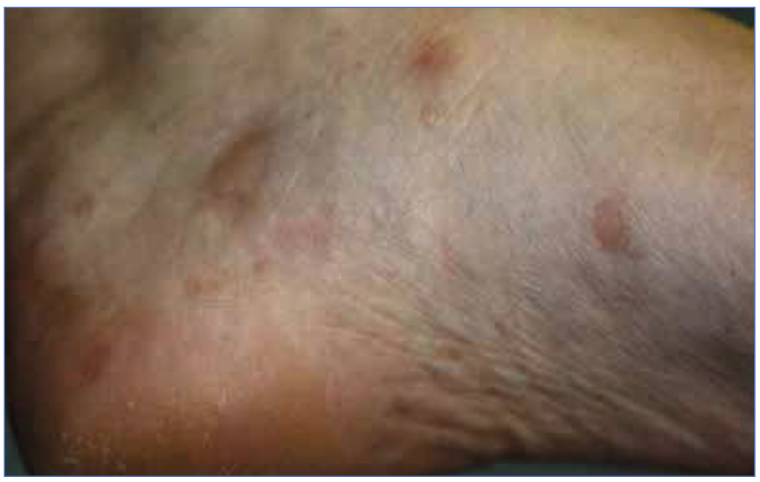
Localized hypomelanosis

COLE DISEASE

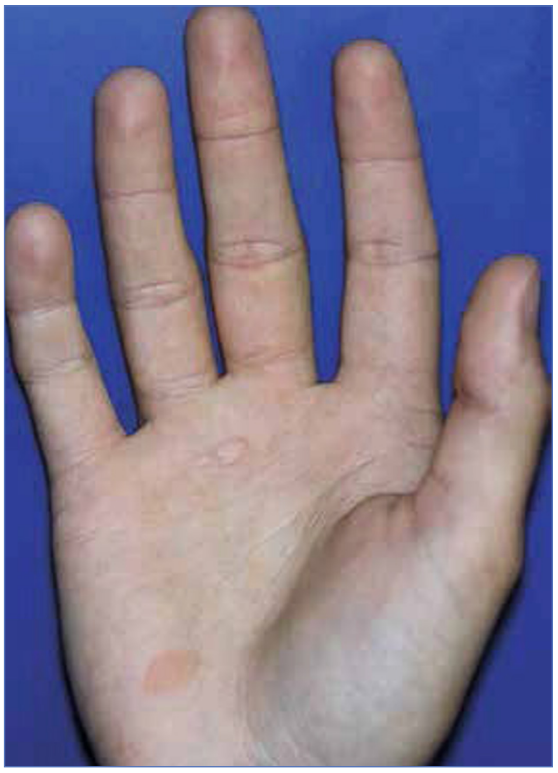
Alain Taieb and Khaled Ezzedine



Cole disease. Hypopigmented macules of the forearm. Note the presence of café-au-lait macules (coll. Alain Taieb).



Cole disease. Mild punctuate and small yellow-brown plaque-like plantar keratoderma (coll. Alain Taieb).



Cole disease. Mild punctuate and small yellow-brown plaque-like palmar keratoderma (coll. Alain Taieb).

OMIM: #615522

GENETICS

Cole disease (COLED) is an autosomal dominant disease caused by heterozygous mutation in the ENPP1 gene on chromosome 6q23.

MOUSE MODEL

None.

EPIDEMIOLOGY

Unknown; very few cases published but possibly under-reported because of limited morbidity.

PATHOPHYSIOLOGY

ENPP1 encodes the ectonucleotide pyrophosphatase/phosphodiesterase I, responsible for the generation of inorganic pyrophosphate, a natural inhibitor of mineralization. All described mutations affect cysteine residues in the somatomedin-B-like domain 2 (SMB2) of the protein, which has been implicated in insulin signalling. Previously, biallelic mutations in ENPP1 were shown to underlie a number of recessive conditions characterized by ectopic calcification but no pigmentation/keratinisation anomalies.

CLINICAL DERMATOLOGICAL PRESENTATION

Onset in infancy of hypopigmented macules.
Localization: primarily on forearms/legs and dorsum of hand-feet.
Mild punctuate and small yellow-brown plaque-like palmoplantar keratoderma, which may involve knees/elbows (pressure areas).
Some hyperpigmented café-au-lait macules may coexist.

EXTRACUTANEOUS SIGNS

X-rays: microcalcifications of tendons, sometimes clinically detectable (calcific tendinopathy). Calcifications of other organs (mammary gland, spleen).

HISTOPATHOLOGY

Skin biopsies of palmoplantar lesions show nonspecific changes including hyperorthokeratosis, hypergranulosis, and acanthosis.
Hypopigmented areas of skin, however, reveal a reduction in melanin content in keratinocytes but not in melanocytes, as well as hyperkeratosis and a normal number of melanocytes. Ultrastructurally, melanocytes show a disproportionately large number of melanosomes in the cytoplasm and dendrites, whereas keratinocytes show a paucity of these organelles, suggestive of impaired melanosome transfer.
Small deposits of calcium in the papillary dermis have been noted inconstantly.

DIFFERENTIAL DIAGNOSIS

- The combination of keratoderma and macular hypopigmentation is pathognomonic.

TREATMENT

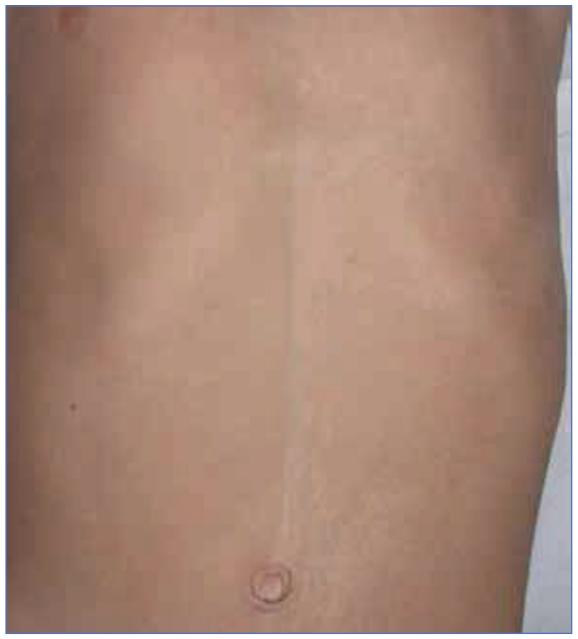
None described so far.

KEY REFERENCES

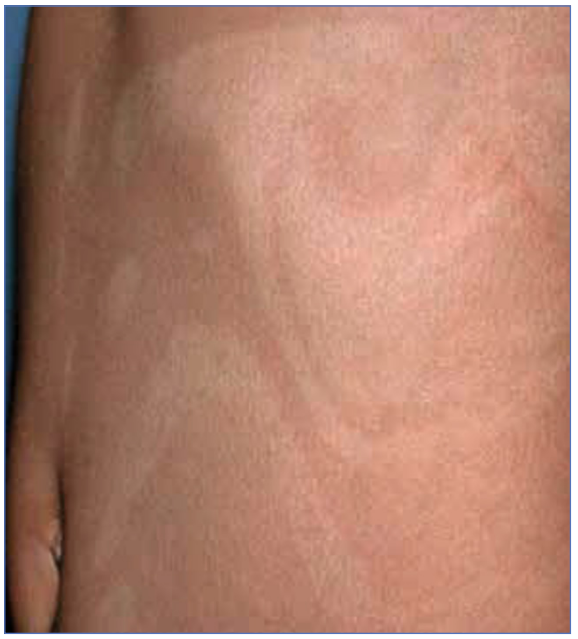
- Cole LA. Hypopigmentation with punctate keratosis of the palms and soles. Arch Derm. 1976;112:998-1000.
- Eytan O, Morice-Picard F, Sarig O, et al. Cole disease results from mutations in ENPP1. Am J Hum Genet. 2013;93:752-57.

MOSAICISMS
HYPOMELANOSIS OF ITO

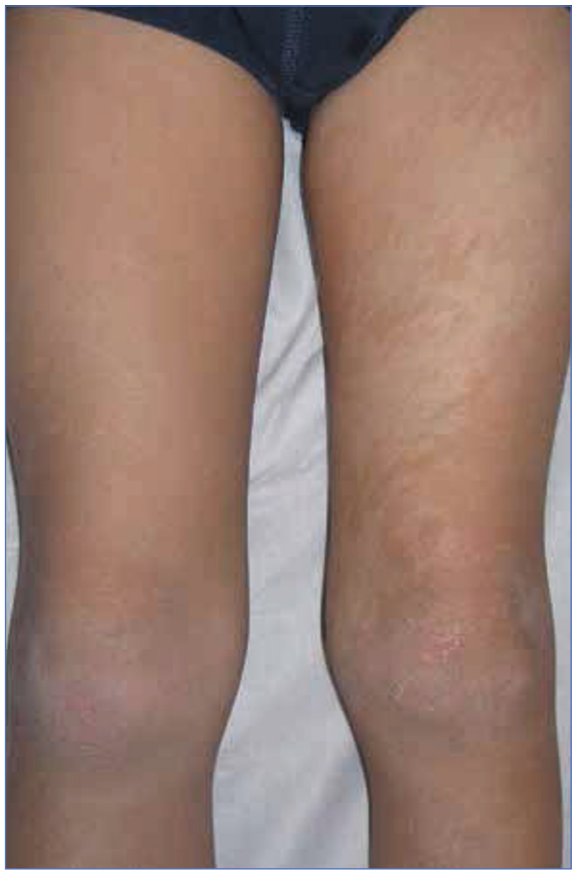
Jean-Philippe Lacour



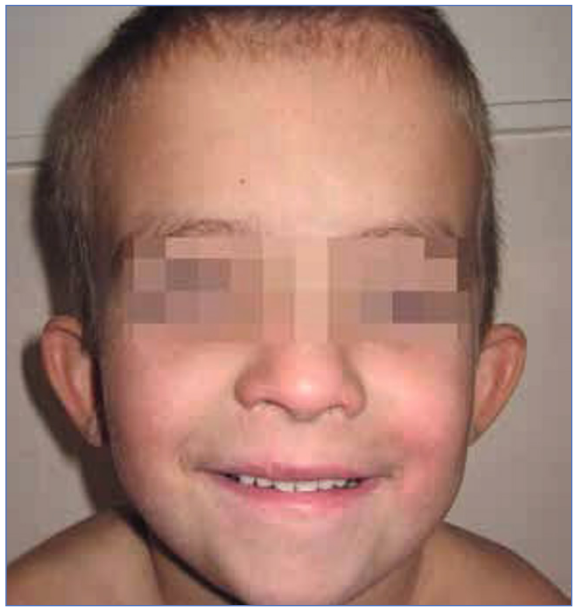
Hypomelanosis of ito. Note the clear demarcation on the mid line.



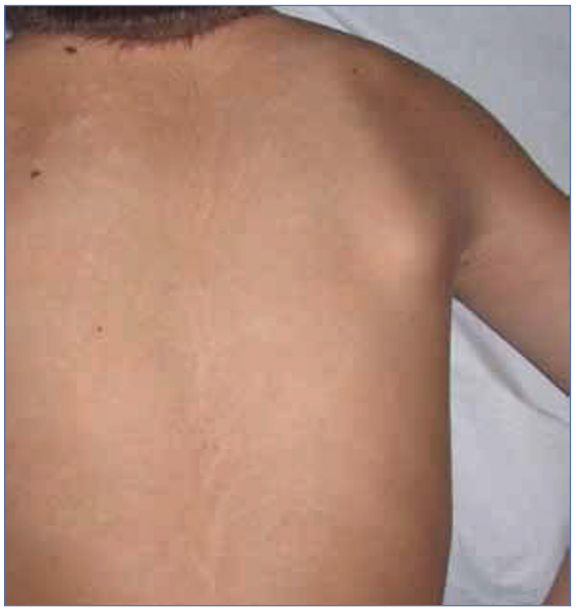
Unilateral hypopigmented whorls following the lines of Blaschko in a patient with hypomelanosis of ito.



Linear unilateral hypopigmention in a patient with hypomelanosis of ito.



A. Young boy with hypomelanosis of ito. Note the low hair line, the hypertelorism, the slight facial asymmetry.



B. Unilateral hypopigmented whorls following the lines of Blaschko on the back of the same boy.

OMIM: # 300337

GENETICS
Generally sporadic disease. Rare autosomal dominant, recessive and X-linked modes of inheritance reported. Cutaneous mosaicism results from of a de novo postzygotic mutation. Some patients may have caryotypic anomalies.

MOUSE MODEL
None.

EPIDEMIOLOGY
Rare disease. One in every 8,000 to 10,000 patients in a general pediatric hospital and 1 in every 1,000 patients in a pediatric neurology service.

PATHOPHYSIOLOGY
Nonspecific pigmentary disorder caused by genetic mosaicism resulting from a de novo postzygotic mutation. The mutation effects are variable, depending on which cells are involved. The hypopigmented lesions result from the presence of different clones of melanocytes that have different abnormalities of melanogenesis, owing to heterogeneous cytogenetic or gene anomalies.

CLINICAL DERMATOLOGICAL PRESENTATION
Hypopigmented areas consisting of bilateral or unilateral whorls and streaks corresponding to the lines of Blaschko. Other types of pigmentary pattern are possible, including: checkerboard pattern, dermatomal or plaque-like arrangement, phylloid pattern, and patchy pattern without midline separation.
It is sometimes difficult to determine where the limits of hypopigmented, normally pigmented or even hyperpigmented skin are.
Possible hair anomalies (low hair line in 7% of cases).

EXTRACUTANEOUS SIGNS
Neurological symptoms: epilepsy, developmental delay, microcephaly, hypotonia, hyperkinesias, autism, deafness.
Ocular signs: microphtalmia, ptosis, symblepharon, strabism, nystagmus, nonclosure of the upper lid, strabismus myopia, amblyopia, corneal opacification, cataract, iridal heterochromia, scleral melanosis, striated patchy hypopigmented fundi, retinal degeneration.
Dental and enamel anomalies.
Skeletal signs: short stature, scoliosis, facial and limb asymmetry, hypertelorism, coarse facies, nose and ear anomalies, pectus carinatum or excavatum, finger and toe anomalies (syndactyly, polydactyly, brachydactyly, clinodactyly).
Cardiac and genital abnormalities may be present.

HISTOPATHOLOGY
Various anomalies described but none are specific to this disease.

DIFFERENTIAL DIAGNOSIS
- Isolated cutaneous mosaicism.
- Nevus depigmentosus (segmental form).
- Incontinentia pigmenti (late phase).
- Tuberous sclerosis complex.
- Lichen striatus.

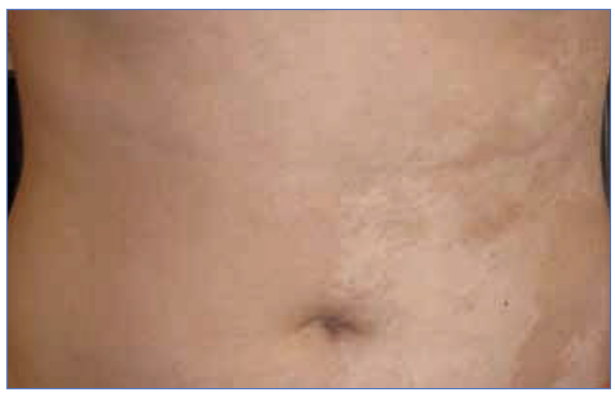
TREATMENT
No specific treatment.
Symptomatic treatment for associated extracutaneous anomalies.

KEY REFERENCES

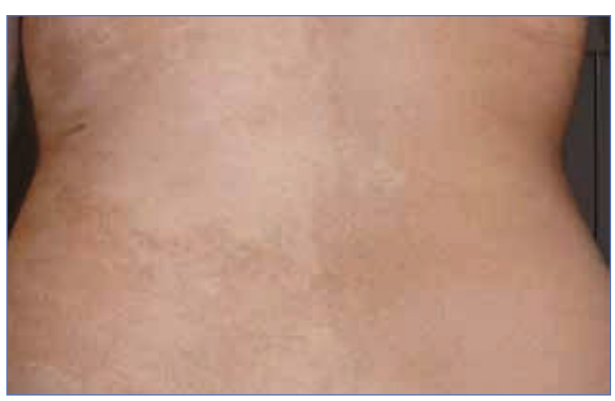
- Happle R. Mosaicism in human skin. Understanding the patterns and mechanisms. Arch Dermatol. 1993;129:1460-70.
- Kuster W, Konig A. Hypomelanosis of Ito: no Entity, but a cutaneous sign of mosaicism. Am J Med Gen. 1999;85:346-50.

MOSAICISMS
OTHER MOSAICISMS WITH HYPOMELANOSIS

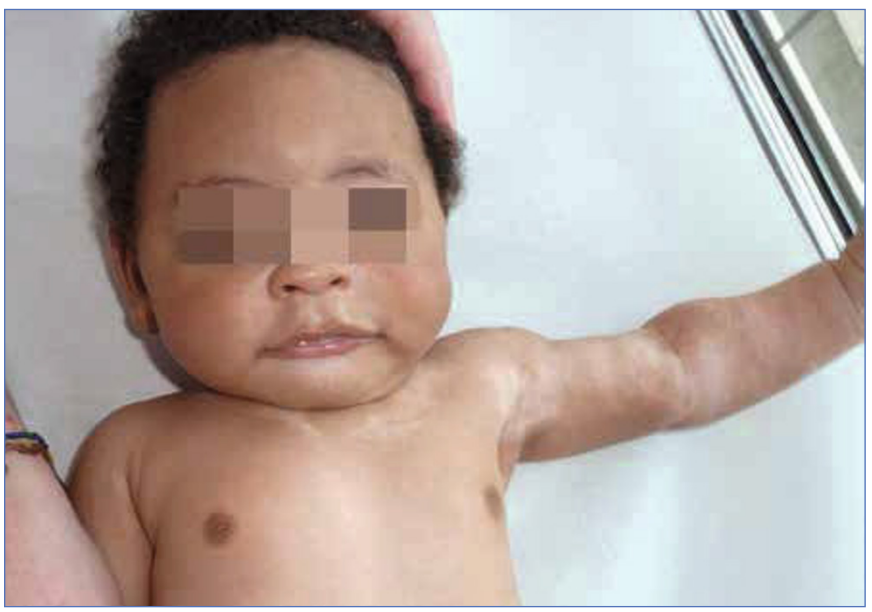
Jean-Philippe Lacour



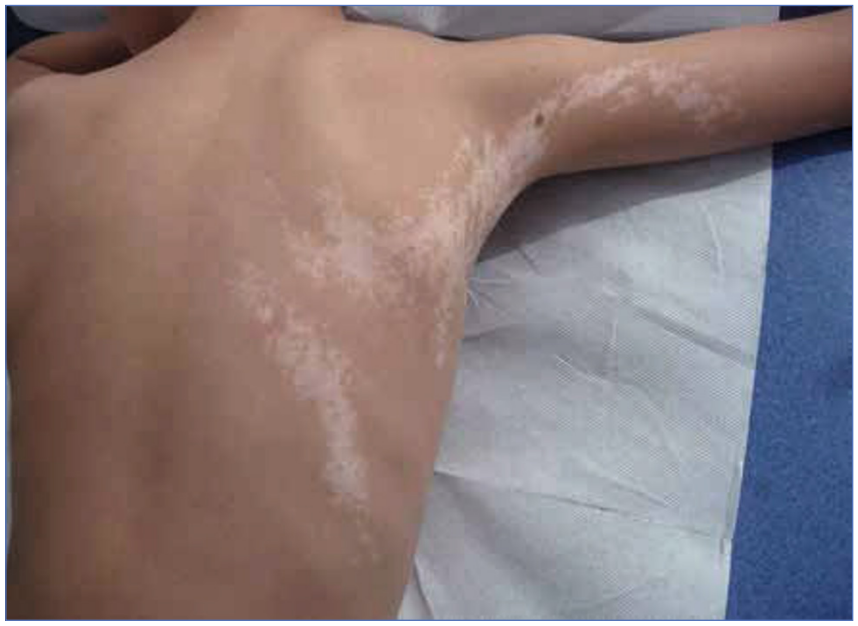
A. Hypopigmented mosaicism. Note the clear demarcation on the middle line.



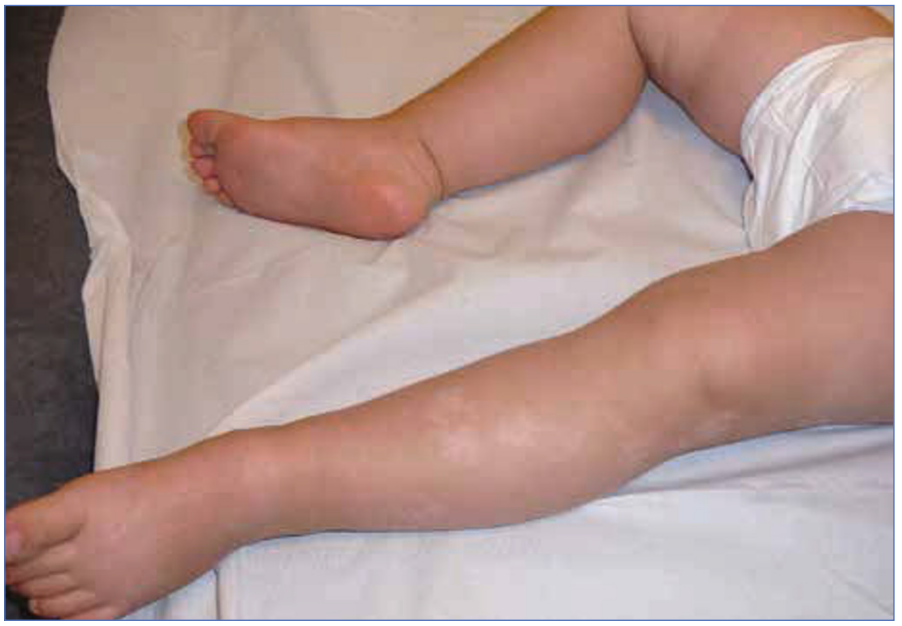
B. The back of the same woman.



Hypopigmented mosaicism in a newborn. The lesions are clearly visible as the boy has a dark skin type, but the hypopigmentation can be difficult to see at birth and is sometimes only visible after one or two summers.



Cutaneous mosaicism with hypopigmented streaks along the lines of Blaschko.



Hypopigmented mosaicism in an infant.

GENETICS
Generally spordaic disease. Cutaneous mocaicism results from a de novo postzygotic muation. Some patients may have karyotypic anomalies.

MOUSE MODEL
None.

EPIDEMIOLOGY
One in every 8,000 to 10,000 patients in a general pediatric hospital.

PATHOPHYSIOLOGY
A nonspecific pigmentary disorder caused by genetic mosaicism limited to cutaneous cells, particularly melanocytes, resulting from a de novo postzygotic mutation. The hypopigmented lesions result from the presence of different clones of melanocytes that have different abnormalities of melanogenesis, owing to heterogeneous cytogenetic or gene anomalies.

CLINICAL DERMATOLOGICAL PRESENTATION
Hypopigmented areas consisting of bilateral or unilateral whorls and streaks corresponding to the lines of Blaschko.
Other types of pigmentary pattern are possible, including: checkerboard pattern, dermatomal or plaque-like arrangement, phylloid pattern, and patchy pattern without midline separation.
It is sometimes difficult to determine where the limits of hypopigmented, normally pigmented or even hyperpigmented skin are.
Possible hair anomalies.

EXTRACUTANEOUS SIGNS
None.

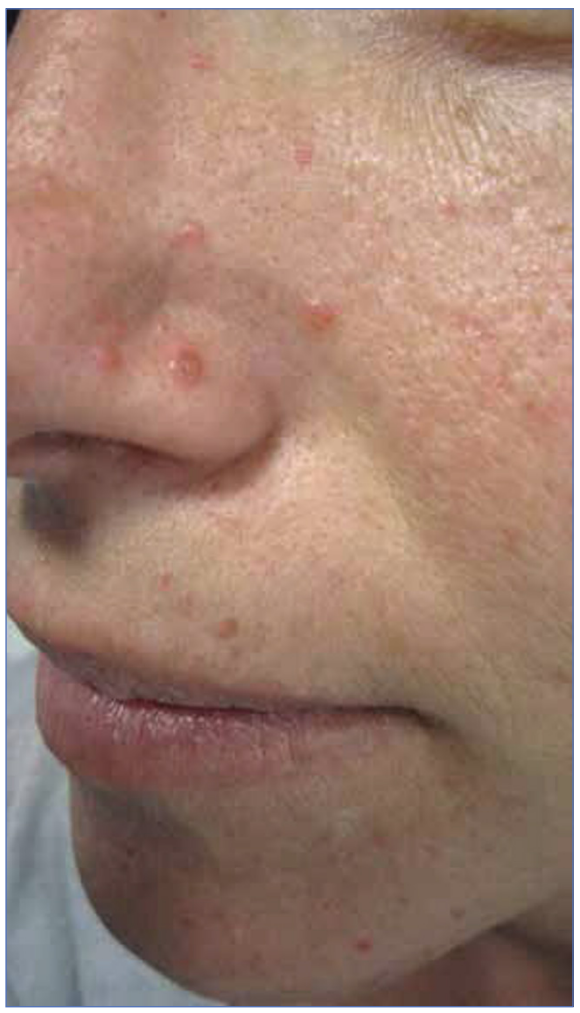
DIFFERENTIAL DIAGNOSIS
- Mosaicism of the Ito type.
- Nevus depigmentosus (segmental form).
- Incontinentia pigmenti (late phase).
- Tuberous sclerosis complex.
- Lichen striatus.

TREATMENT
No specific treatment.

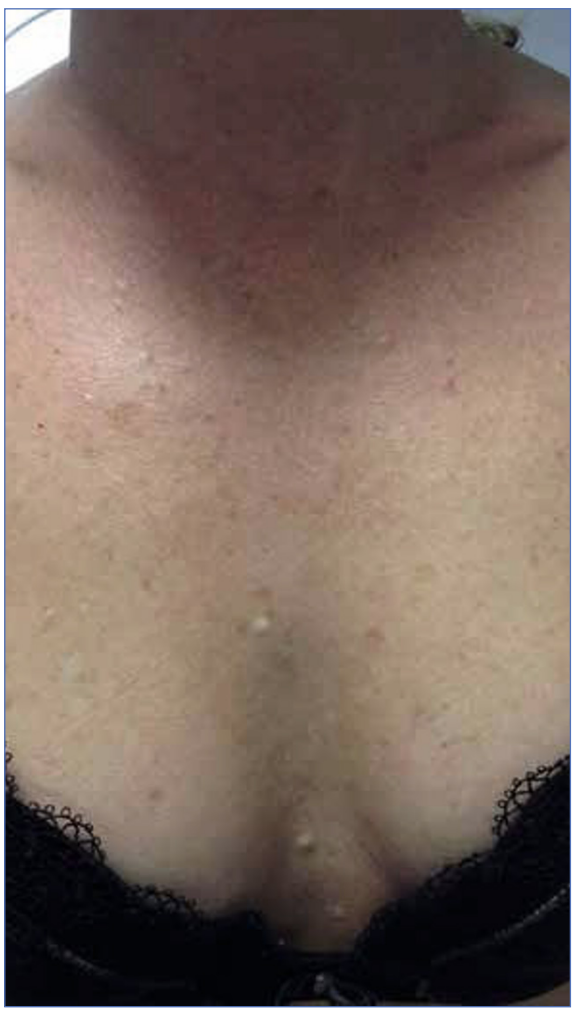
KEY REFERENCES

- Happle R. Mosaicism in human skin. Understanding the patterns and mechanisms. Arch Dermatol. 1993;129:1460-70.
- Kuster W, Konig A. Hypomelanosis of Ito: no entity, but a cutaneous sign of mosaicism. Am J Med Gen. 1999;85:346-50.

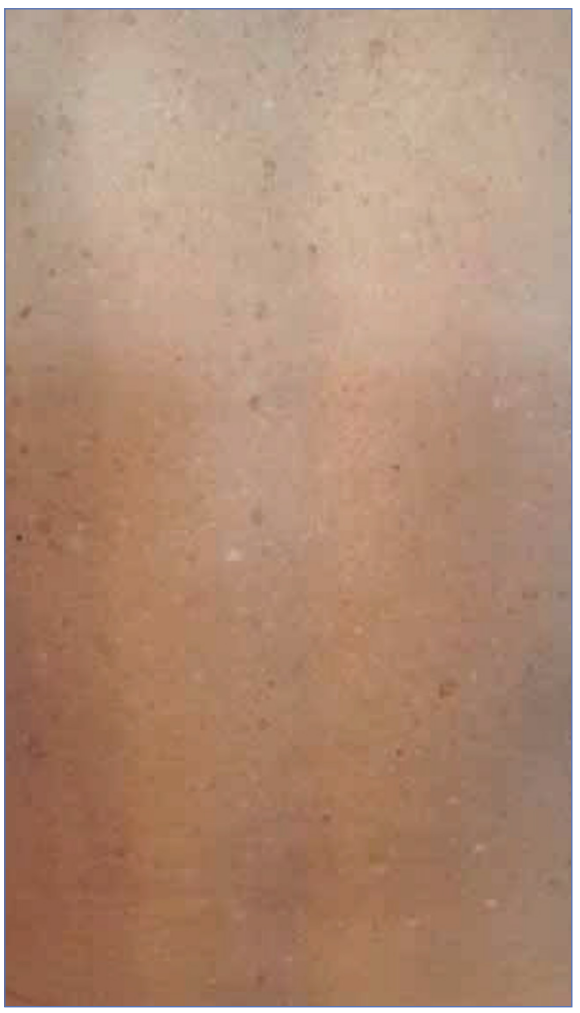
MULTIPLE ENDOCRINE NEOPLASIA, MEN1



Multiple angiofibromas on the face in a woman with MEN1.



Multiple collagenomas on the trunk.



'Confetti-like' hypopigmented macules in the same patient.

OMIM: #131100

SYNONYMS
Multiple endocrine adenomatosis, Wermer syndrome.

GENETICS
Autosomal dominant disorder caused by heterozygous mutation in the MEN1 gene on chromosome 11q13.

MOUSE MODEL
Mouse homolog Men1.

EPIDEMIOLOGY
Prevalence 1 out of 30,000 persons.
No race or sex predilection.

PATHOPHYSIOLOGY
The MEN1 gene encodes a protein called menin. Menin regulates transcription, proliferation, and genome stability. Affected individuals inherit one altered copy of the MEN1 gene from an affected parent, but the tumors lose the remaining copy (the wildtype allele) as a somatic event. Thus, the inheritance pattern is autosomal dominant, but the mechanism of tumorigenesis is recessive.

CLINICAL DERMATOLOGICAL PRESENTATION
Dermatologic manifestations are usually the first observed. The earliest cutaneous and endocrine tumors appear in the teenage years but the symptoms of endocrine tumors take many years to develop.
Angiofibromas (telangiectatic skin-colored papules) and collagenomas (firm skin-colored or hypopigmented round papules) are the two main skin manifestations. They are mostly located on the central face of the face, and on trunk, respectively.
Lipomas and gingival papules can be observed.
Pigmentary lesions are not rare:
- Solitary hypomelanotic macules.
- 'Confetti-like' hypopigmented macules.
- Café-au-lait macules (less than 3).

EXTRACUTANEOUS SIGNS
Endocrine tumors: parathyroid glands, enteropancreatic neuroendocrine system, anterior pituitary gland.

HISTOPATHOLOGY
Reduction of the number and size of melanosomes, mostly in the unmelanized stage are observed in hypomelanotic macules. Increased amount of melanin in the epidermis with an increased number of melanocytes in the café-au-lait spots.

DIFFERENTIAL DIAGNOSIS
- Tuberous sclerosis.
- Birt-Hogg-Dubbe syndrome.
- Cowden disease.

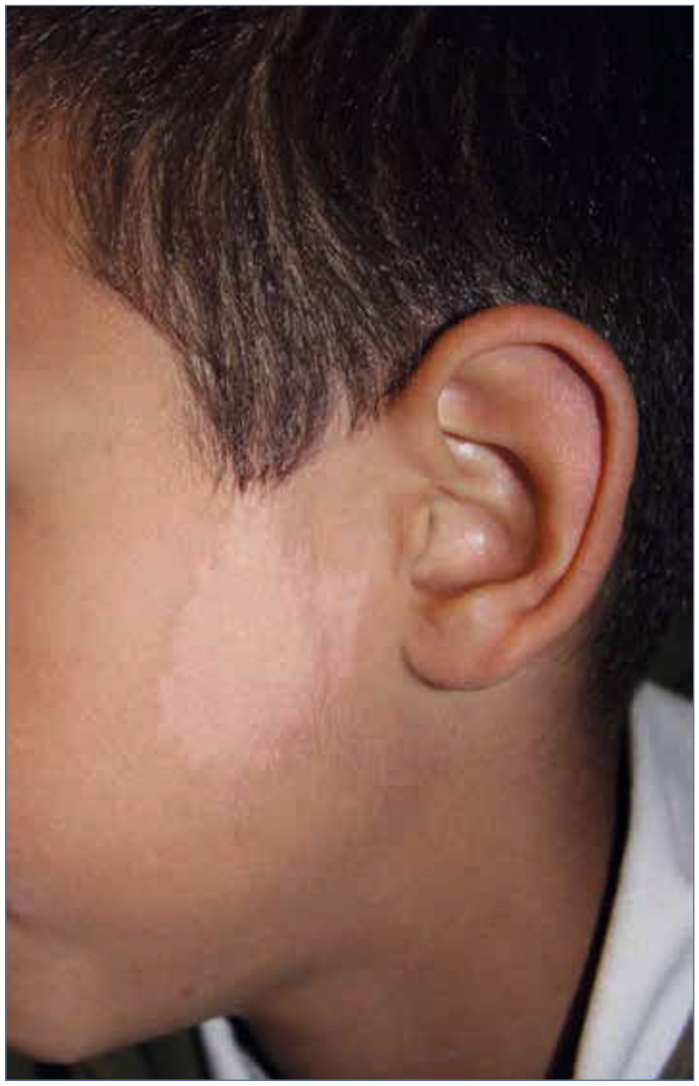
TREATMENT
Endocrinologist consultation and follow-up.
Surgical excision, dermabrasion, pulsed-dye laser, erbium or CO_2 lasers can be proposed to remove skin tumors.

KEY REFERENCES

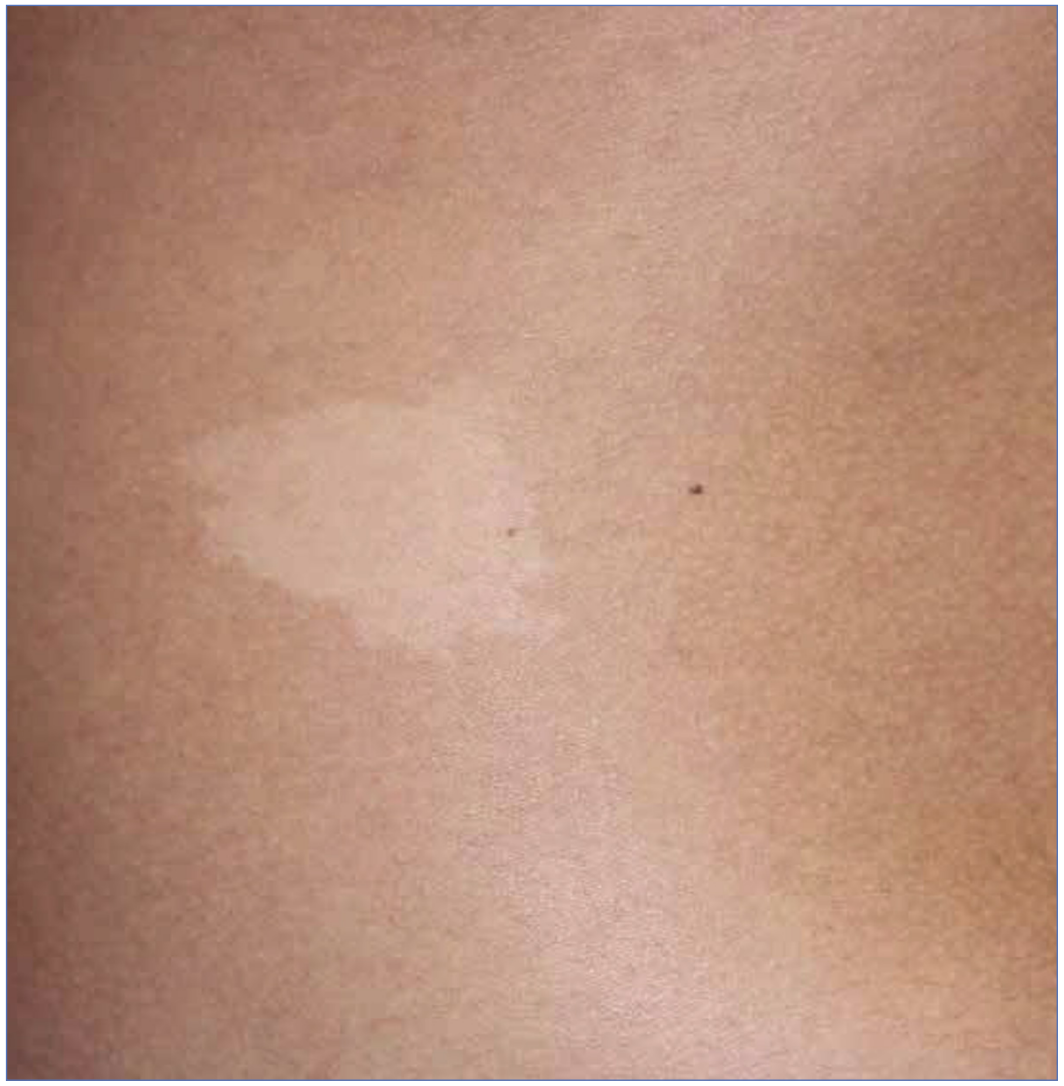
- Chandrasekharappa SC, Guru SC, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science. 1997;276:404-6.
- Darling TN, Skarulis MC, Steinberg SM, Marx SJ, Spiegel AM, Turner M. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. Arch Dermatol. 1997;133:853-7.
- Vidal A, Iglesias MJ, Fernández B, Fonseca E, Cordido F. Cutaneous lesions associated to multiple endocrine neoplasia syndrome type 1. J Eur Acad Dermatol Venereol. 2008;22:835-8.

NEVUS DEPIGMENTOSUS

Nanja van Geel



Nevus depigmentosus on the cheek of a young boy (coll. Nanja van Geel).



Nevus depigmentosus of the lumbar region.

EPIDEMIOLOGY

Not rare.

PATHOPHYSIOLOGY

The exact cause of nevus depigmentosus is still not clearly understood. It is based on abnormalities in the transfer of melanosomes from melanocytes to keratinocytes thereby resulting in the characteristic cutaneous hypopigmented spots.

CLINICAL DERMATOLOGICAL PRESENTATION

Well-circumscribed hypopigmented macule, sometimes with an irregular border.
Commonly becomes visible from birth or in the first year of life and usually does not change in shape thereafter.
In contrast to what its name suggests, the nevus depigmentosus presents itself as a hypopigmentation rather than a depigmentation.
According to some authors, there are three clinical variants: the isolated form (solitary and well defined lesions), a segmental form (unilateral, band-shaped lesions, sometimes Blaschkoid distribution) and a systematized form (extensive whorls and streaks of hypopigmentation, following the lines of Blaschko [see: hypomelanosis of Ito or pigmentary mosaicism]).

EXTRACUTANEOUS SIGNS

The disease is primarily limited to the skin, however whenever a Blaschkoid pattern is seen, associated neurological and musculoskeletal abnormalities may be present. Developmental disorders and epilepsy are the most commonly reported problems (see pigmentary mosaicism/ hypomelanosis of Ito).

HISTOPATHOLOGY

Histological studies on lesional skin compared with perilesional normal skin shows a marked reduction in melanin, but variable results in the number of melanocytes (normal to reduced).

DIFFERENTIAL DIAGNOSIS

- Vitiligo.
- Nevus anaemicus.

TREATMENT

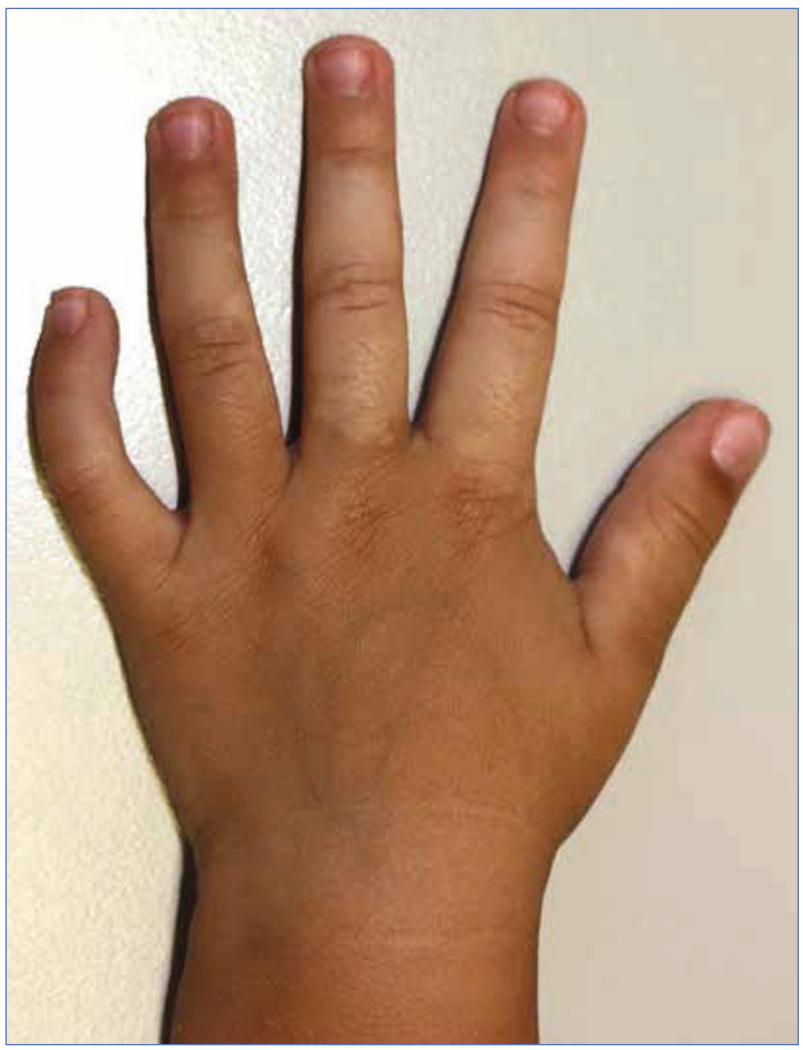
Camouflage.
Surgical grafting has been reported in the literature, although with variable results (poor to good repigmentation) and possible recurrence during follow up.

KEY REFERENCES

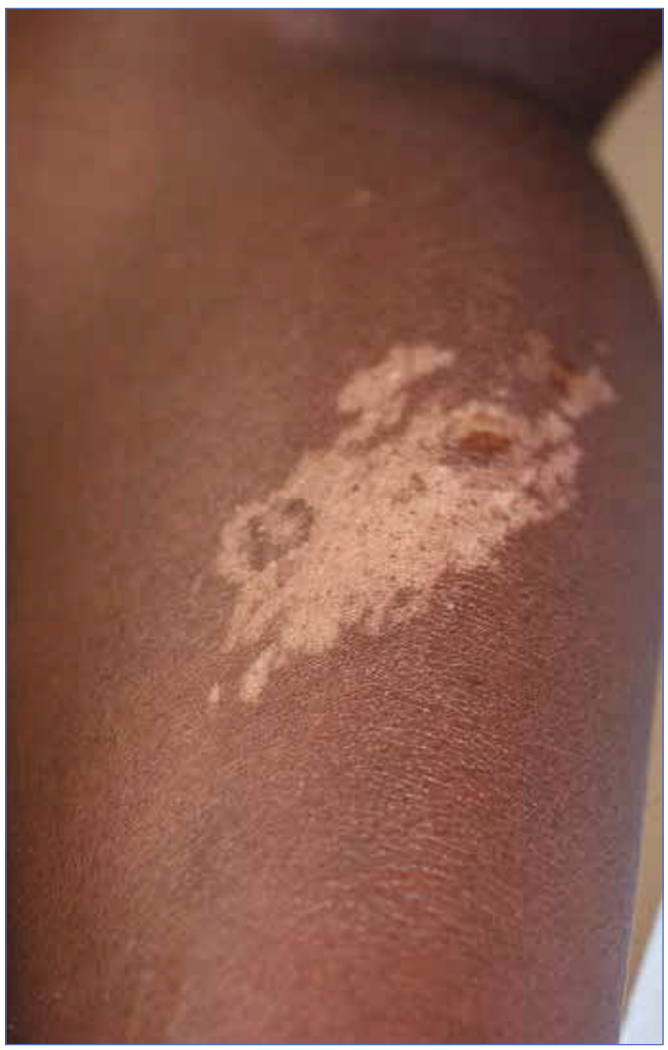
- Kim SK, Kang HY, Lee ES, Kim YC. Clinical and histopathologic characteristics of nevus depigmentosus. J Am Acad Dermatol. 2006;55:423-8.
- Happle R. Mosaicism in human skin. Understanding the patterns and mechanisms. Arch Dermatol. 1993;129:1460-70.

NEVUS DEPIGMENTOSUS

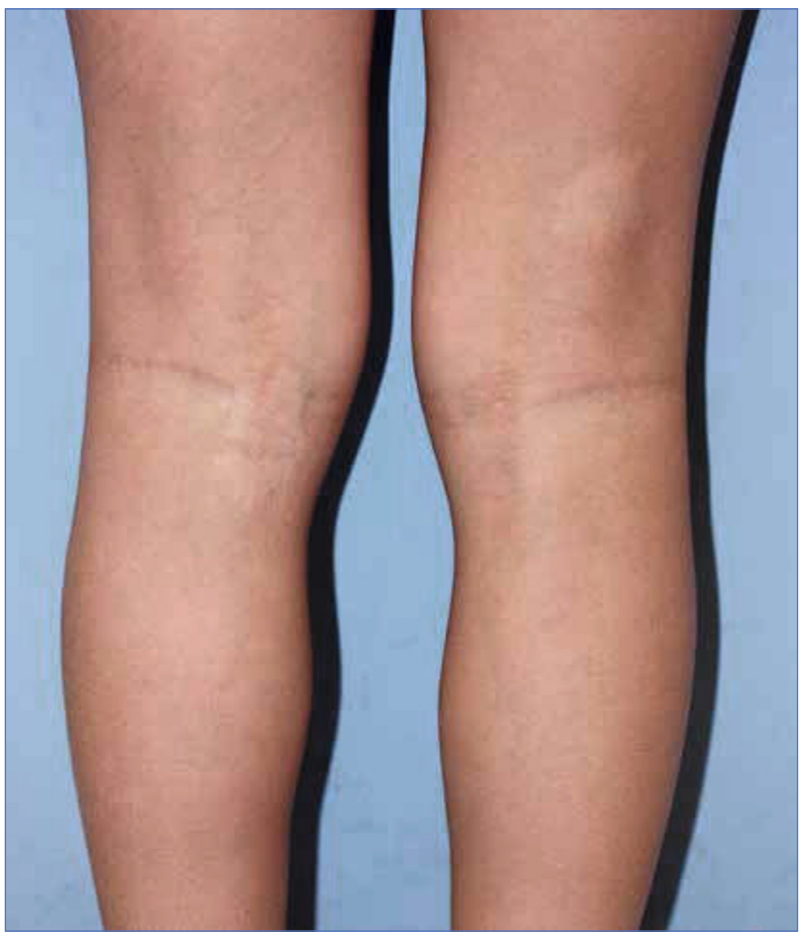
Nanja van Geel



Kissing nevus depigmentosus of the hand.



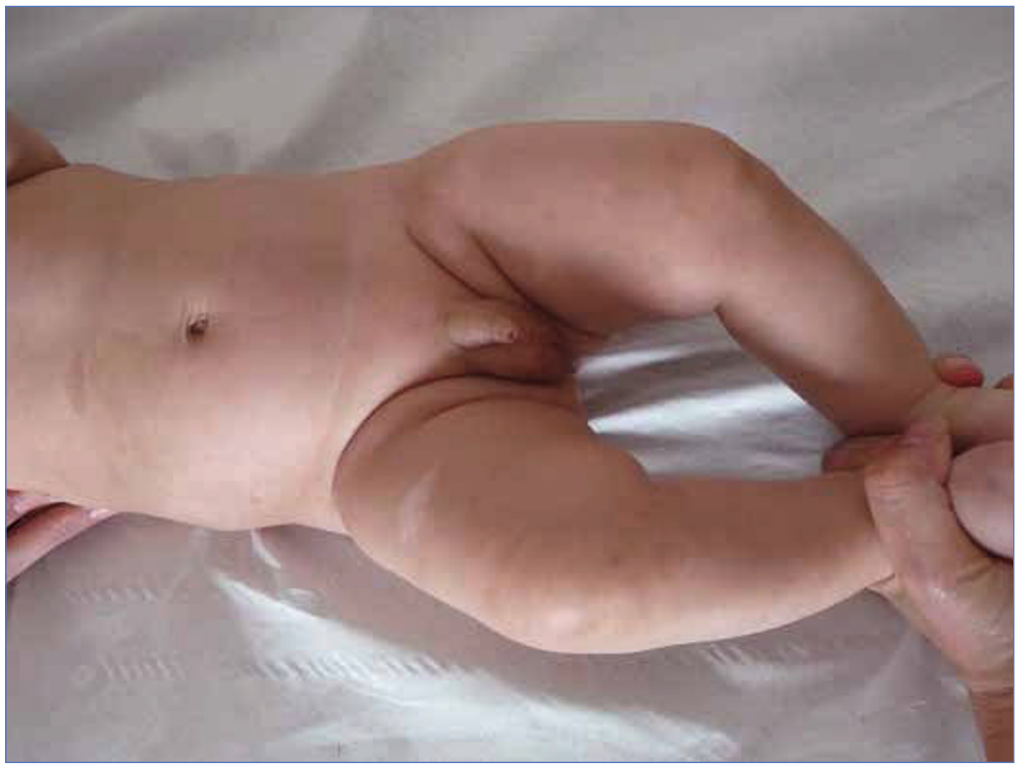
Nevus depigmentosus on a dark skin patient. Note that the lesion is hypopigmented and not depigmented.



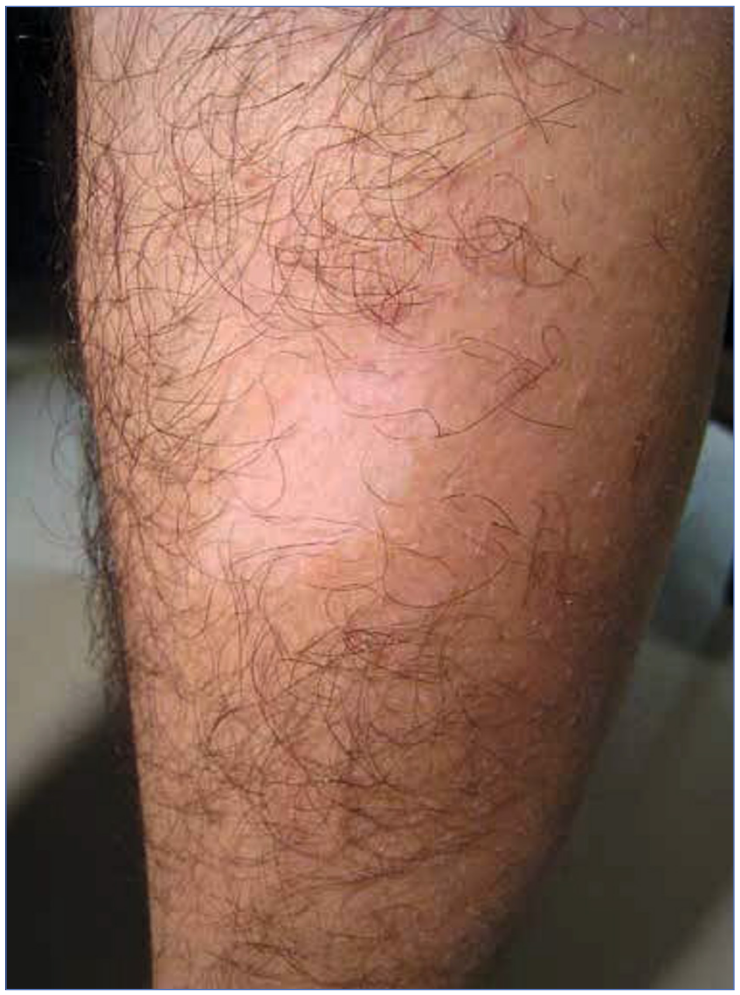
Multiple nevus depigmentosus.

TUBEROUS SCLEROSIS COMPLEX

Jean-Philippe Lacour



Association of 'ash leaf' hypopigmented macules and café-au-lait spots in an infant with tuberous sclerosis complex.



Typical pattern of hypopigmented macule ('ash leaf') in a man with tuberous sclerosis complex.

OMIM: #191100, #613254

GENETICS

Autosomal dominant disorder but the majority of cases are sporadic. Results from inactivating mutations in either TSC1 (9q34,37) or TSC2 (16p13.3.38). Both mutations are equally represented in familial tuberous sclerosis complex (TSC), but mutations in TSC2 are more common in sporadic cases.

MOUSE MODEL

Tsc2 (+/–) mouse.

EPIDEMIOLOGY

Prevalence is 8.8 out of 100,000.
Incidence is 1 in 6,000 to 10,000 births.

PATHOPHYSIOLOGY

TSC1 encodes a 130-kDa protein TSC1/hamartin37 and TSC2 encodes a 200-kDa protein TSC2/tuberin, which contains a C-terminal GTPase activating protein domain (GAP). Hamartin and tuberin bind to each other to form a functional heterodimer (TSC2:TSC1). TSC1 or TSC2 encoded proteins modulate cell growth and proliferation via the inhibition of the mammalian target of rapamycin (mTOR) signaling cascade. Mutations lead to constitutive activation of the mTOR pathway leading to the growth of hamartomas.

CLINICAL DERMATOLOGICAL PRESENTATION

Hypomelanotic macules 'ash leaf' spots (enhanced by Wood's lamp examination but not completely depigmented as compared to vitiligo or piebaldism lesions).
Variable number.
Localization: Trunk and limbs.
'Confetti-like' macules (enhanced by Wood's lamp examination), usually on the legs, and poliosis are less commonly observed but are also suggestive of the diagnosis.
Café-au-lait macules may be observed.
Facial angiofibromas (Koenen tumors).
Forehead fibrous plaque.
Shagreen patches (lumbosacral area).
Periungual fibromas (Koenen tumors).
Molluscum pendulum.

EXTRACUTANEOUS SIGNS

Neurological abnormalities: West syndrome, epilepsy (60 to 90% of patients), neurocognitive dysfunction, developmental delay, autism. These result from structural brain abnormalities such as: cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas.
Renal lesions (50 to 80% of patients): angiomyolipomas with a risk of spontaneous hemorrhage, renal cysts, renal cell carcinoma, and oncocytomas.
Pulmonary lymphangioendotheliomatosis (female patients exclusively).
Cardiac rhabdomyomas (50 to 70% of infants).
Retinal astrocytic hamartomas (50% of patients).

HISTOPATHOLOGY

Reduction of the number and size of melanosomes, mostly in the unmelanized stage. Reduction of the number of melanosomes transferred to keratinocytes.

DIFFERENTIAL DIAGNOSIS

- Nevus depigmentosus.
- Vitiligo.
- Piebaldism.

TREATMENT

Symptomatic treatment.
Antagonists of the mTOR pathway such as rapamycin and related compounds are potential new therapeutic options for TSC patients.

KEY REFERENCES

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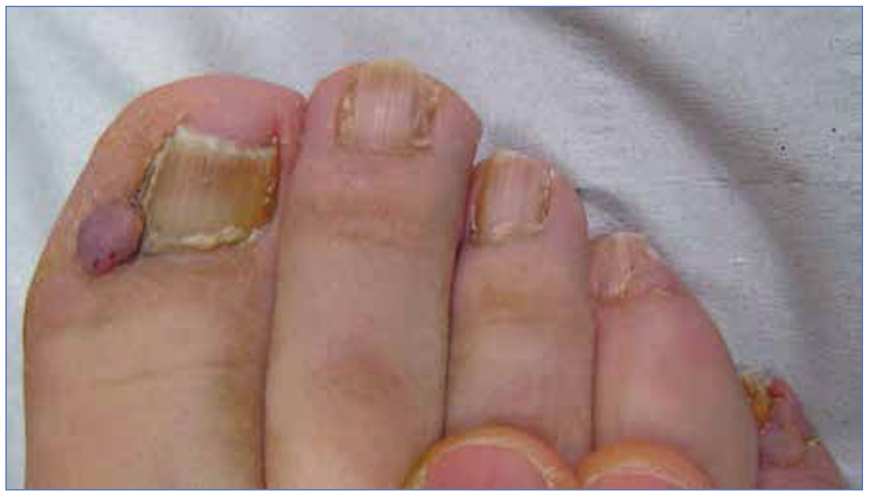
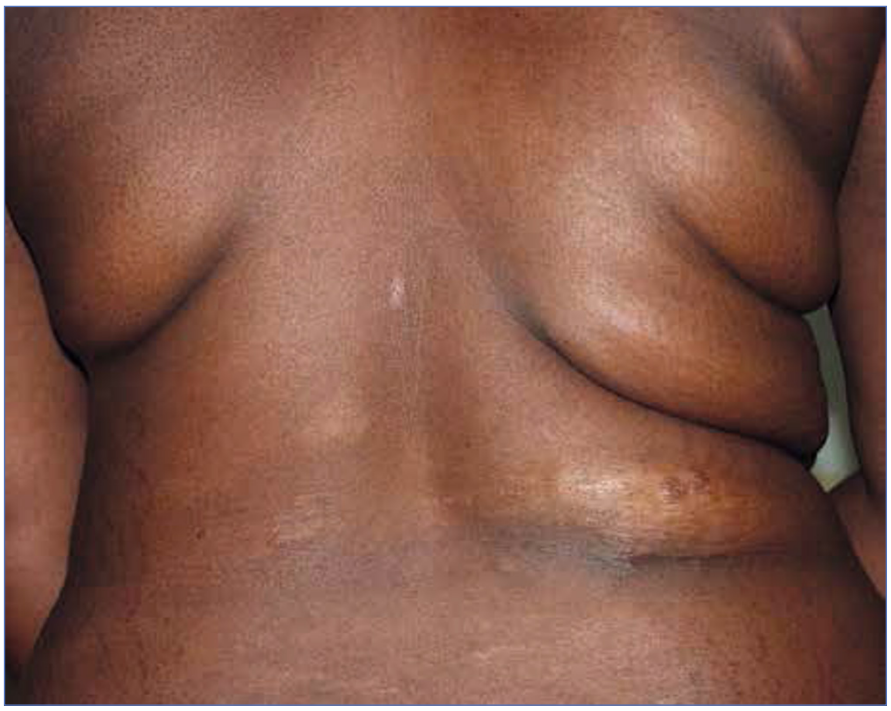
- Schwartz RA, Fernandez G, Kotulska K, Jozwiak S. Tuberous sclerosis complex: Advances in diagnosis, genetics, and management. J Am Acad Dermatol. 2007;57:189-202.

TUBEROUS SCLEROSIS COMPLEX

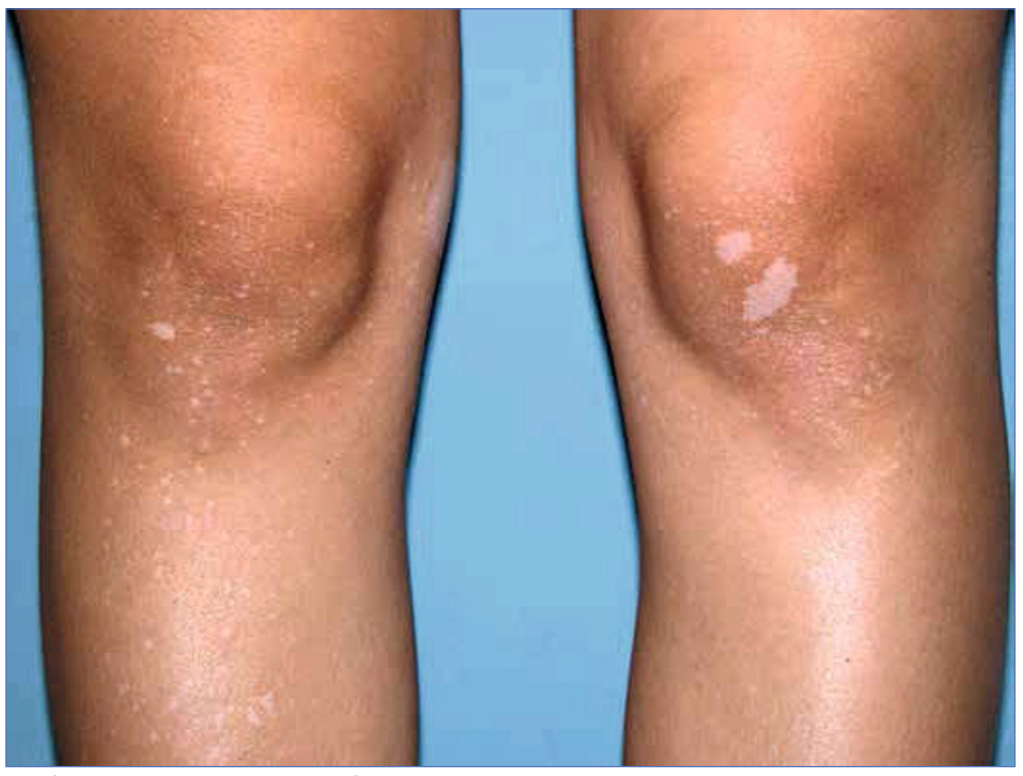
Jean-Philippe Lacour



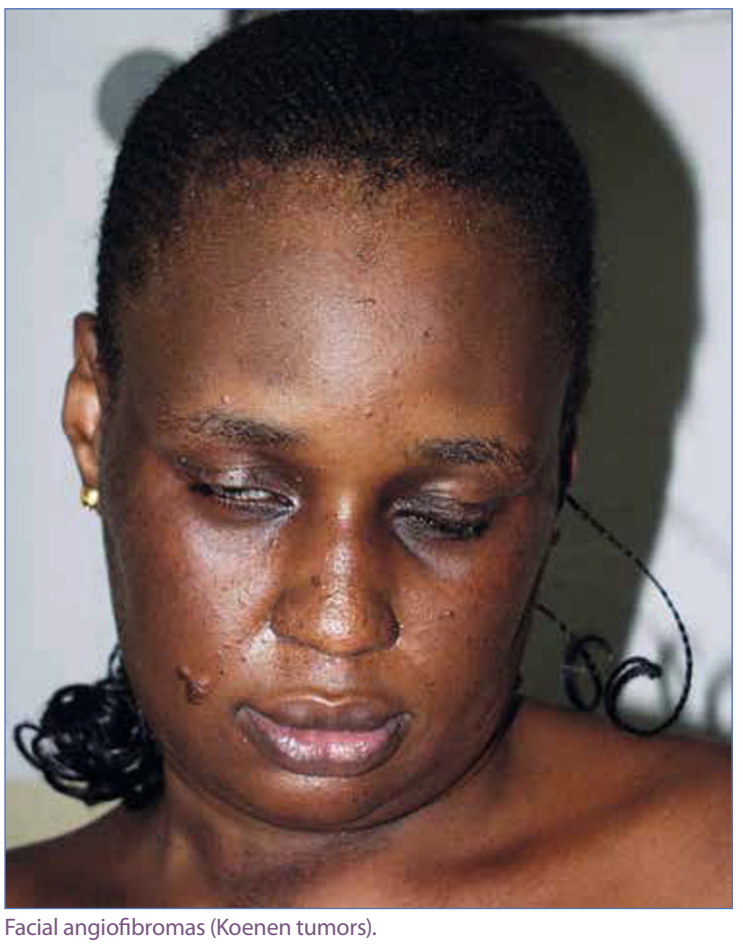
Periungual fibromas (Koenen tumors).



Shagreen patches (lumbosacral area).



'Confetti-like' macules on the legs of a child with tuberous sclerosis complex.



Facial angiofibromas (Koenen tumors).