

Hypomelanosis of Ito vs Pigmentary Mosaicism: a challenging diagnosis



CENTRO HOSPITALAR DE LISBOA CENTRAL, EPE

Antunes D.¹, Kay T.¹, Cabete J.², Marques B.³, Brito F.³, Correia H.³, Nunes L.¹,

¹ Serviço de Genética Médica, Hospital Dona Estefânia, CHLC, EPE

² Serviço de Dermatologia, Hospital dos Capuchos, CHLC, EPE

³ Unidade de Citogenética, Departamento de Genética Humana, INSA, I.P.

E-mail: diana.antunes@chlc.min-saude.pt



GOVERNO DE PORTUGAL
MINISTÉRIO DA SAÚDE

Instituto Nacional de Saúde
Doutor Ricardo Jorge

INTRODUCTION:

The term Hypomelanosis of Ito (HI) (OMIM #300337) has been applied to individuals with skin hypopigmentation along the lines of Blaschko, a non-random developmental system of linear and/or whorled streaks first described in 1901 as a constant pattern of cutaneous markings characterizing the distribution of various linear and segmental skin disorders.

HI still represents a challenging disorder for clinicians and a controversial issue in the medical literature. In fact, even though Ito's original report in 1952 described HI as purely cutaneous disease, subsequent case reports and case series have reported a 33-94% association with multiple and sometimes severe extracutaneous manifestations mostly of the central nervous system (CNS) leading to frequent characterization as a neurocutaneous disorder. Neurologic involvement is present in more than 70% of patients who mainly present mental retardation and epilepsy. Different seizures types have been reported, such as myoclonic, complex partial, and generalized tonic or tonic-clonic, or infantile spasms. Other features include cognitive/behavioural deficits, epilepsy, musculoskeletal abnormalities like hemihypertrophy, scoliosis, finger abnormalities, and ophthalmologic defects, such as strabismus or nystagmus, cardiac defects and hearing impairment have also been reported, among others. Neuroimaging may reveal a wide spectrum of defects, such as dysplasia, and vascular malformations.

Several models of inheritance have been proposed. A number of reports claimed familial occurrence and single gene inheritance, however there is still no consistent finding and a monogenic cause for HI seems so far unlikely. A number of cytogenetic studies has revealed an enormous range of mosaic chromosomal abnormalities in some but not all affected individuals.

SUBJECT

A 5-year-old girl was referred for observation by Medical Genetics for dyschromia, *minor* dysmorphic features, ventricular septal heart defect and slight learning difficulties. The patient already had undertaken a peripheral blood karyotype that was normal. The parents brought a development evaluation made by a multidisciplinary team that reported that the girl presented a IQ below average. No other relevant personal or familiar history.

At observation we recognized the hypopigmented patches and strikes resembling the pattern of Blaschko's lines. The minor dysmorphic features included a round face, sparse eyebrows, long eyelashes, broad nares, tented upper lip, dysplastic low-set ears and prognathism. Other anomalies were also noticed like strabismus, short neck with low posterior hairline, simian palm crease on right hand, persistency of fetal pads, and mild genu valgum/recurvatum. The patient had well adjusted growth (Height:110cm - P75, Weight:21Kg - P50, Head Circumference:51cm - P75)



Figure 1 – Clinical photographs showing (A;B;C) the hypopigmented pattern of along the Blaschko's lines and (D) of the hands showing the persistency of fetal pads and a simian palm crease on right hand.

METHODS

A skin biopsy for histopathological and cytogenetic studies was performed on a hypopigmented patch and a magnetic resonance imaging (MRI) of CNS was requested.

GTL-chromosome banding was performed on peripheral blood sample, for confirmation, and skin biopsy using standard methods.

Fluorescence *in situ* hybridization (FISH) was done on fixed cells according to standard procedures using a centromeric probe for chromosome 18 (D18Z1) and the whole chromosome probe 18 (wcp18).

RESULTS

Histopathological study of the skin was inconclusive, revealing no alteration in distribution of melanocytes or on intensity of pigmentation.

CNS MRI showed no alteration.

Peripheral blood karyotype, like before, showed no alteration.

Cytogenetic study on the skin biopsy revealed the presence of a mosaic. Besides the normal cell line (56%) it was detected a abnormal line with monosomy of chromosome 18 and presence of a marker chromosome (44%).

FISH analysis identified the marker as a derivative of chromosome 18, comprising the centromeric region and a small portion of euchromatic material.

The karyotype was establish as: 46,XX,-18,+mar[22]/46,XX[28].ish der(18)(wcp18+,D18Z1+).

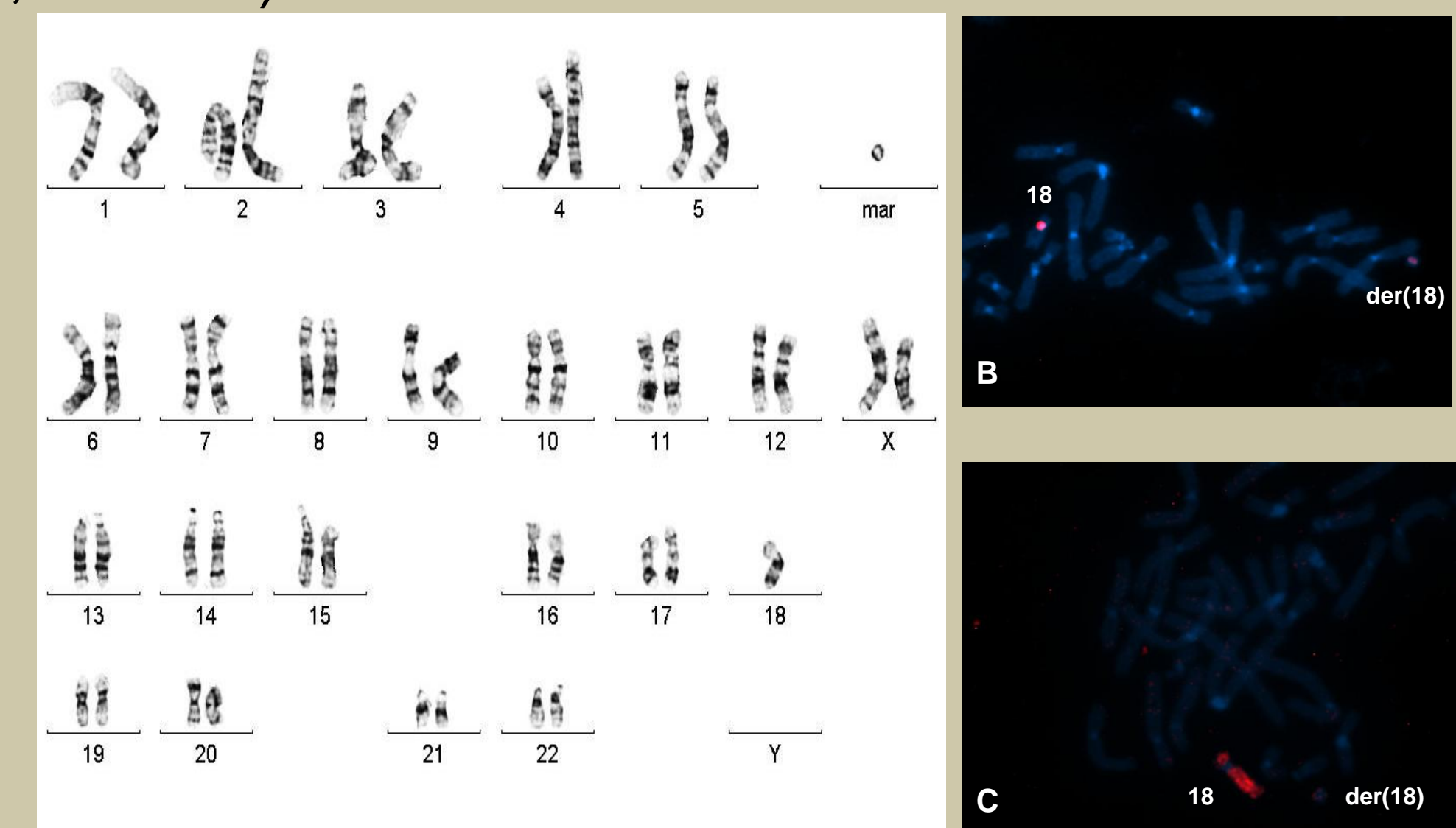


Figure. 2 – (A) G-banded karyotype of the abnormal cell line showing the marker chromosome (mar); (B) FISH with the centromeric chromosome 18 probe (D18Z1) showing that the mar chromosome derives from chromosome 18 (der18); (C) FISH with whole chromosome 18 painting probe (wcp18) showing a small amount of euchromatin at the der(18).

DISCUSSION

It has been suggested by several authors that HI is not a single condition but rather a nonspecific manifestation (i.e., phenotype) reflecting genetic mosaicism which likely disrupts expression or function of pigmentary genes. In the London Dysmorphology Database there are 107 different syndromes (including HI) under the same entry "patchy depigmentation of skin". Following the hypothesis that the chromosomal abnormalities reported specifically disrupt pigmentary genes some authors suggest that HI would be better designated as "Pigmentary Mosaicism" (PM), referring to a clone of skin cells with a decreased ability to produce pigment, PM can be a useful term to encompass all these different phenotypes.

Although numerous cases of mosaicism concerning chromosome 18 were previously described, this specific cytogenetic anomaly was not yet reported to the best of our knowledge. The mild phenotype presented by this patient suggests that the abnormal cell line may have a low expression. Nevertheless, the lost genetic material in the abnormal cell line raises several questions about future outcomes. Because there are several tumor-suppressor genes located on chromosome 18 there is theoretical concern of a predisposition to certain malignancies. The risk for cancer would depend on the percentage of the abnormal cell line in the respective tissues of concern (colon, pancreas or bone) which is impossible to predict. Prenatal diagnosis in case of a future pregnancy should be offered to the patient regarding the risk of gonadal mosaicism.

This case illustrates the challenge of a diagnosis when facing a variety of phenotypes and the difficulty of genetic counseling. It also reinforces the importance of karyotyping other tissues besides peripheral blood if there is a strong clinical suspicion of mosaicism.

REFERENCES

Jackson K E, Tsien F, Marble M. 2000. Phenotypic Features in a Boy with Monosomy 18 Mosaicism. *Am J Med Genet* 95:229-232
 Molho-Pessach V, Schaffer J V. 2011. Blaschko lines and other patterns of cutaneous mosaicism. *Clin Dermatol* 29:205-255
 Ruggieri M, Pavone L. 2000. Hypomelanosis of Ito. Clinical Syndrome or Just Phenotype? *J Child Neurol*. 15:635-644

Taibjee S M, Bennett D C, Moss C. 2004. Abnormal pigmentation in hypomelanosis of Ito and pigmentary mosaicism: the role of pigmentary genes. *Brit J Dermatol* 151:269-282
 Yardin C. 2001. First Familial Case of Ring Chromosome 18 and Monosomy 18 Mosaicism. *Am J Med Genet* 104:257-259
 Winter RM, Baraitser M. 2007. *The London Dysmorphology Database*. Oxford: Oxford University Press