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# CLINICAL, CYTOGENETIC AND MOLECULAR CHARACTERIZATION OF TWO CASES OF MOSAIC RING CHROMOSOME 13

*BY A. UWINEZA [1], G. PIERQUIN [1], S. GAILLEZ[1], M. JAMAR [1], A.C. HELLIN [1], J.H. CABERG [1] AND V. BOURS [1]*

**Summary:** *Clinical, cytogenetic and molecular characterization of two cases of mosaic ring chromosome 13:* The occurrence of mosaic ring chromosome 13 is rare. The mechanism of ring chromosome formation is usually associated with loss of genetic material. We report 2 cases of mosaic ring chromosome 13, resulting in deletion of 13qter. The first patient, a 15 year-old boy, presented a delayed psychomotor development, mental retardation, dysmorphic features and bleeding disorders associated with a de novo terminal 13q34 deletion. The second case was a foetus of 31 weeks with prenatal diagnosis of severe malformation such as holoprosencephaly, congenital cardiac defects, gastro-intestinal abnormalities with intrauterine growth retardation, the molecular analysis showed a de novo deletion encompassing the region 13q31.3-q34.

**Key-words**: Ring chromosome – 13q deletion – Mosaicism – Array-CGH.

## INTRODUCTION

Mosaic ring chromosome 13 syndrome is a rare chromosomal abnormality. Ring chromosomes frequently arise following a breakage in the short and long arms of a chromosome followed by fusion of the broken ends, or from the union of one broken chromosome end with the opposite telomere region leading to loss of genetic materials (14). However, the ring chromosome phenotypes are very variable due to the primary deletion associated with ring formation and secondary to the ring chromosome instability that can give rise to loss or gain of material (9). The severity of clinical features will depend on the size of the deleted region along chromosome 13. Recent studies using Array-CGH have tried to correlate more precisely the phenotype to the genotype and to specify the 13q deletion syndrome characterized by moderate to severe mental and growth retardation, no specific dysmorphic features, digital malformations, neural tube defects such as holoprosencephaly, corpus callosum agenesis, cardiac or renal malformations, ambiguous genitalia, penoscrotal transposition with anal atresia (5, 12, 17).

We report 2 unrelated patients with de novo mosaic ring chromosome 13. We performed a genome-wide array-based CGH in order to delimit exactly the extension of the 13 chromosome deleted regions.

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# METHODS AND RESULTS

## CLINICAL PRESENTATION

### Patient 1

The proband, a 15 year-old boy, was the only child of healthy non consanguineous parents. He was born at term by normal delivery following a normal pregnancy. At nine years, he was first seen at the genetic counselling department for evaluation of his mental retardation, blood disorders characterized by frequent nasal bleeding and moderate hematuria. He had a past medical history of choanal atresia.
The physical examination showed a weight of 29.5kg (50th centile), height of 137 cm (90th centile) and head circumference of 49.5 cm (below the 3rd centile). He presented discrete dysmorphic features (Fig. 1) characterized by: large forehead, microcephaly, hypertelorism, large external ears, prominent nasal bridge, short philtrum, webbed neck and moderate asymmetry of the lower limbs. He had moderate mental retardation associated with speech impairment.

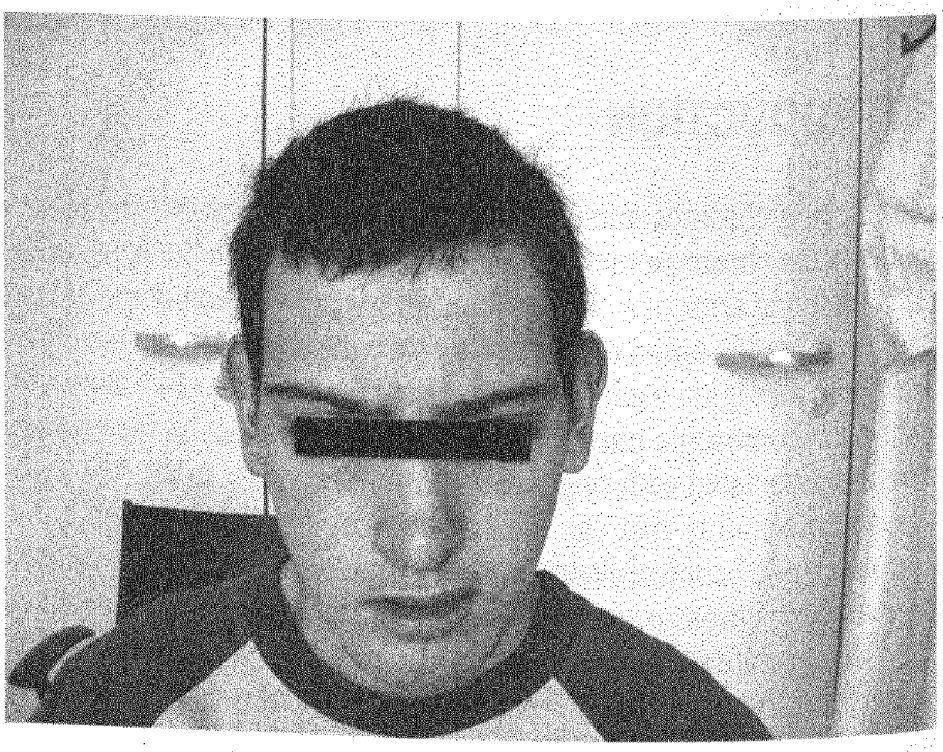

*Figure 1:* Picture of the 15 year-old boy showing his dysmorphological features.

### Patient 2

A 19 year-old (G1, P0) woman and her unrelated husband were referred for genetic counselling, because an ultrasonography performed at 31 weeks of gestation revealed a single foetus with severe intraute-

rine growth retardation, holoprosencephaly (confirmed by MRI), and an aortic arch malposition. Amniocentesis was suggested for prenatal chromosomal analysis, which revealed a 13q deletion. At the 33-week gestational age, cordocentesis at placental cord insertion was done followed by induced termination of pregnancy. Foetal autopsy was performed and the external physical examination of a 1515g foetus showed (Fig. 2): hypertelorism, bulbous nose, short philtrum, open-mouth appearance, large forehead and ambiguous external genitalia. Internal examination revealed: a right aortic arch, absence of brain's interhemispheric scissures and agenesis of the corpus callosum.

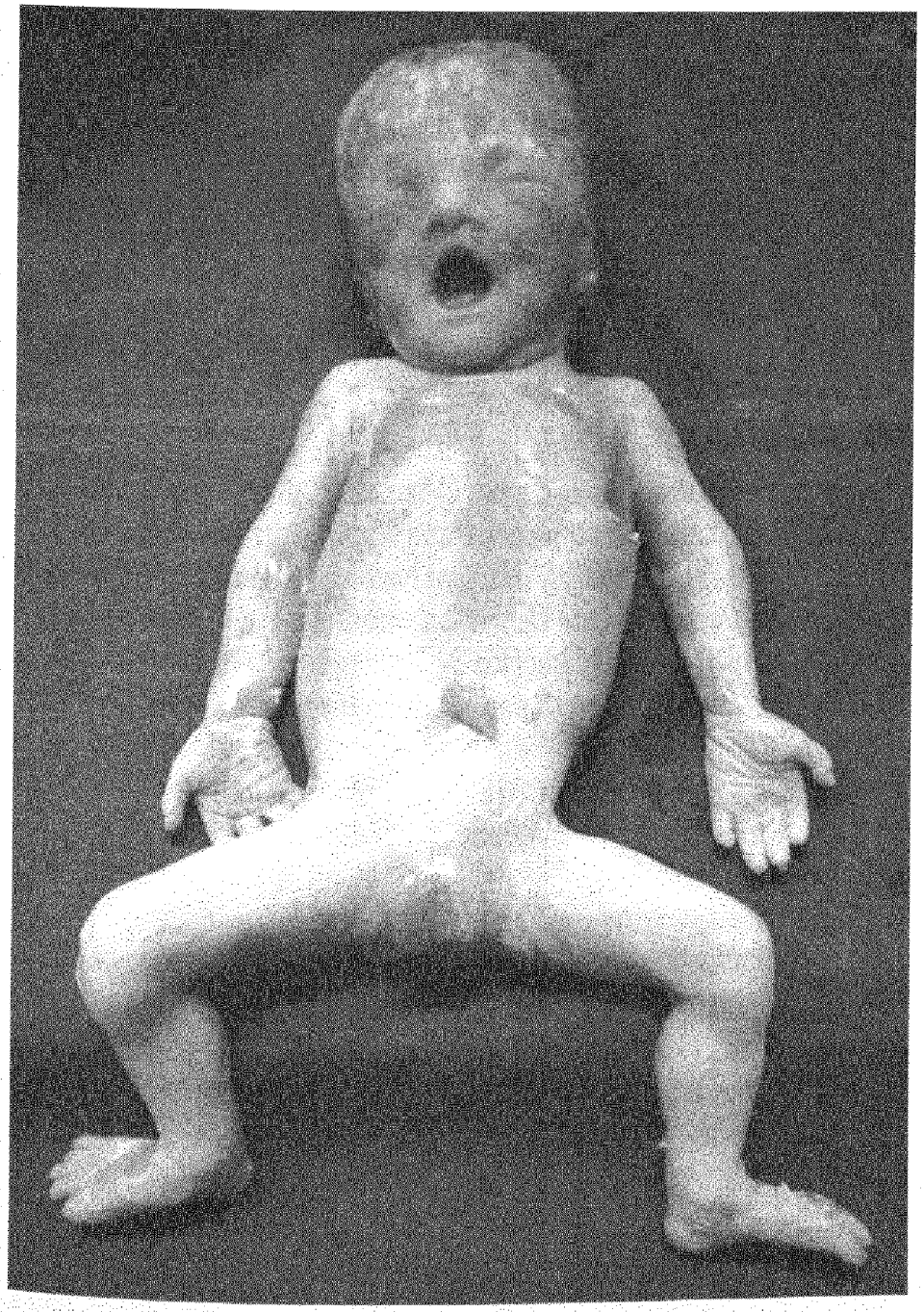

*Figure 2*: A fetus of 33 week of gestation. Note hypertelorism, bulbous nose, short philtrum, open-mouth appearance, large forehead and ambiguous genitalia.

## CYTOGENETIC ANALYSIS

### Patient 1

Conventional chromosome analyses was performed with a resolution of 550 bands (GTG banding) on peripheral lymphocytes and revealed a mosaic karyotype with 2 different cell lines mos 45,XY, -13[10]/46,XY, r(13)[40] (Fig. 3).

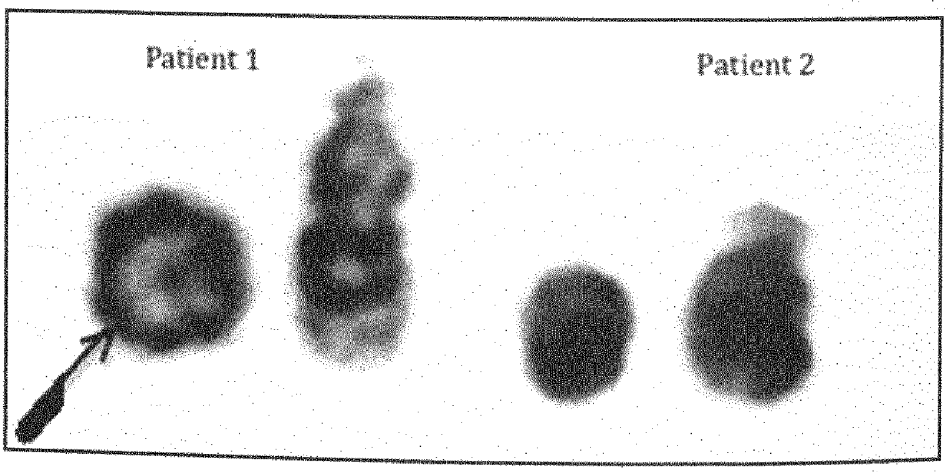


*Figure 3:* G-banded of the ring chromosome 13 and the normal chromosome 13 on both patients.

### Patient 2

The foetal karyotype analysis on G-banding analysis was done on long-term cultured ammiotic cells and showed a karyotype of mos 46,XY,r(13)[8]/45,XY,-13[5]. The analysis of the product of miscarriage showed a different karyotype mos46,XY,r(13)(q32q34)[18]/ 46,XY,dic r(13)(q32q34)[2]dn (ISCN 2009) (Fig. 3).
The parents' karyotypes were normal in both patients.

## MOLECULAR ANALYSIS

Genomic DNA was extracted from peripheral blood (patient 1) and from cordocentensis (foetus), using standard procedures of phenol chloroform.
Array CGH analysis using the Affymetrix Cytogenetics Whole-Genome 2.7 M Array were performed as described before (15) and according to the manufacturer's standard protocols (http://ww.affymetrix.com) (Affymetrix, Inc., Santa Clara, CA, USA). Affymetrix CEL files were analysed by Affymetrix Chromosome Analysis Suite (CHAS) version 1.1.
For the first patient, the analysis identified two deletions in the 13q34 region one of 350 kb and another of 3740 kb. The second patient had a large deletion of 21,687 Mb in the region 13q31.3-q34 (Fig. 4).

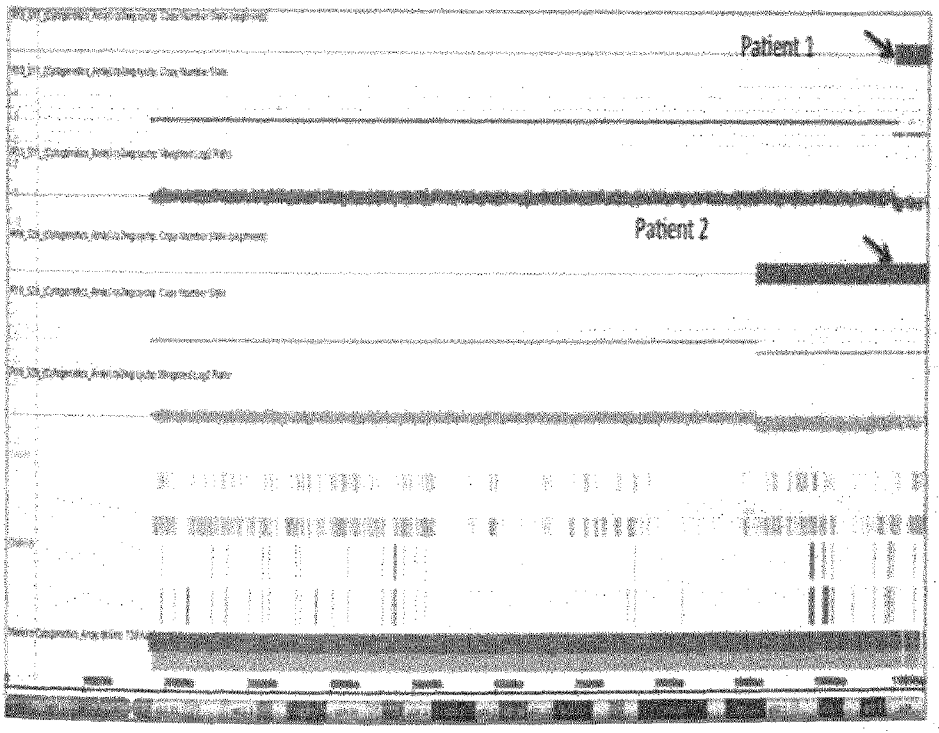


*Figure 4:* Genome-wide array CGH result : showing the 13q34 microdeletion.

## DISCUSSION

We characterised two patients with an unusual form of mosaicism with two cell lines. The first patient present two terminal deletions of the ring chromosome 13, one of 350 kb and another microdeletion of about 3740 kb in the 13q34 region, identified by the array-CGH. The spectrum of 13q deletions is currently divided into 3 groups based on genotype-phenotype correlations: those proximal to 13q32 (group 1), those including 13q32 (group 2), and those distal to 13q32 (group 3) (6).
According to this clinical classification, our first patient fits broadly within the third group, which include patients with more distal deletions involving bands q33–34. Those patients usually show growth delay and severe mental retardation, without severe malformations. However our patient presents additional features that have not been described in the literature like asymmetry of lower limbs. His blood disorder characterized by frequent nasal bleeding and episode of hematuria had already been reported (4, 8, 10) and might be explained by reduced level of Factors VII and X in patients, which might result from haploid insufficiency (8, 13). Our patient presented also moderate mental retardation and microcephaly. Microcephaly was frequently associated with terminal deletion of the chromosome 13 (3, 5, 18). Kirchhoff M and alter defined the terminal 6 Mb region of chromosome 13q as a microcephaly critical region. It has been proposed that haploinsufficiency of one or more genes located in this region (ARHGEF7,

UPF3B, SOX1) is responsible for microcephaly and the malformations of cortical development. These anomalies are due to abnormal neuronal migration, in individuals with 13q deletions (12, 18). Choanal atresia has been described in patients with13q deletion but two had interstitial deletion of the long arm of the chromosome 13 and another one with 13q32 deletions (2, 7, 12), there may be a gene implicated in the choanal formation.

The second case also showed the presence of two cell lines: one, containing the ring, is monosomic for the distal portion of chromosome 13, the other, containing a dicentric double-ring chromosomes, that is trisomic for the same portion. The CGH array showed a large deletion of 21,687Mb in the 13q31.3-q34 regions. The foetus had more severe malformations such as holopresencephaly, agenesia of the corpus callosum, cardiac malformation, ambiguous genitalia and dysmorphic features. These were consistent with the second group of patients (6). Brown *et al.* defined the 13q32 as a region critical for embryonic development. As this deletion causes a distinct phenotype that includes brain malformations, it has been suggested that cerebral malformations such as holoprosencephaly spectrum and cerebral midline defects of the 13q deletion syndrome are linked to ZIC2 haploinsufficiency (3, 16). Our patient presented also a right aortic arch, Huang *et al.* proposed that the 13q33.1-34 region might be one of the regions responsible for congenital heart disease, and they suggested the locus for congenital heart minimal deletion of 6 Mb (11). The fœtus presented sexual ambiguity. The specific gene implicated in the development of ambiguous genitalia has however not been classified yet, but can be associated with the EFNB2 gene (1).

In conclusion, we describe two patients with the mosaic ring chromosome 13 syndrome. This report shows the wide spectrum of patients carrying this chromosomal abnormality and the importance of realizing the analysis of array CGH to allow a better correlation between the phenotype and genotype.

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