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Tetrasomy 13q Mosaicism Associated With Phylloid Hypomelanosis and Precocious Puberty

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Abstract

Various forms of pigmentary dysplasias have been known to be associated with chromosomal mosaicism. One of these disorders, known as phylloid hypomelanosis, has been found to be predominantly associated with abnormalities in chromosome 13. Most of the reported literature involves mosaic trisomy 13 with clinical evidence of abnormal pigmentation in the form of leaf-like or oblong achromic macules following Blaschko's lines. Here, we report on an 8-year-old girl with phylloid hypomelanosis and precocious puberty who was found to have mosaicism for tetrasomy 13q in the form of inverted dup(13)(q21) on her skin fibroblasts as well as peripheral blood karyotype. A higher resolution (244K) chromosomal microarray was done on DNA from skin fibroblasts confirming the breakpoint and gain of distal 13q, which made her tetrasomic for 13q21-qter. This is the first-ever reported association of tetrasomy 13q with phylloid hypomelanosis and precocious puberty. Our report further emphasizes the need to exclude any type of abnormalities of chromosome 13 in patients with phylloid hypopigmentation.

Keywords

phylloid hypomelanosis; mosaic tetrasomy 13q; microarray; precocious puberty; developmental delay

INTRODUCTION

Mosaicism refers to the occurrence in an individual of two or more cell populations that are karyotypically or genotypically different and yet are derived from a single zygote. An association between pigmentary anomalies and chromosomal mosaicism has been reported since the 1960s [Ferrier et al., 1964; Zuelzer et al., 1964; Teplitz et al., 1967; Varela and Sternberg, 1969]. Since then several cases reporting associations between pigmentary patterns such as linear, whorled or patchy and hypo- or hyperpigmented skin and chromosomal mosaicism have been published. Cytogenetic alterations such as mosaicism for trisomy 18, diploidy/triploidy, sex chromosomal aneuploidy, mosaic trisomy 13 and tetrasomy 12p have been reported in the literature to be associated with pigmentary anomalies [Happle, 1993, 2000; Horn et al., 1997].

Various forms of pigmentary dysplasias have been described occurring along the lines of Blaschko, in a checkerboard pattern, phylloid pattern and patchy pattern without midline separation [Happle, 1995]. Pigmentary mosaicism is a term used to encompass all of these different types of pigmentary patterns [Taibjee et al., 2004]. Among these mosaic patterns, there have been only a few reports of the phylloid presentation (Greek phyllon = leaf, eidos = form) in the literature. The multiple leaf-like patches resemble a Jugendstil painting (named after the avant-garde periodical in Germany, *Die Jugend* (“Youth”), which featured Art Nouveau designs characterized by highly stylized, flowing, curvilinear designs often incorporating floral and other plant-inspired motifs), and they exhibit dorsal and ventral midline separation. In contrast to the more known hypomelanosis of Ito (or “mosaic hypomelanosis” as seen in Hypomelanosis of Ito), which represents a cutaneous symptom of many different chromosomal abnormalities, phylloid hypomelanosis has been found to be predominantly associated with abnormalities in chromosome 13 [Happle, 2001]. Phylloid hypomelanosis has been described as a neurocutaneous syndrome that is characterized by the phylloid pattern of skin pigmentation associated with developmental delay or mental retardation.

The pathogenesis of pigmentary mosaicism has been explained by various hypotheses. These include co-migration of genetically different cell populations, functional X-chromosome mosaicism, spreading of X inactivation to autosomes in balanced X; autosomal translocations, partial activation or silencing of pigmentary genes by transposons, genetic imprinting and phenotypic reversion [Taibjee et al., 2004]. In the review by Taibjee et al., a unifying hypothesis proposed that chromosomal abnormalities found in pigmentary mosaicism specifically disrupt expression or function of pigmentary genes.

Here, we present a case of a patient with phylloid hypomelanosis as a clinical feature not previously reported to be associated with mosaic tetrasomy 13q.

CLINICAL REPORT

The patient is a Latin American girl born to nonconsanguineous parents who was brought to medical attention at 3 years of age due to her abnormal skin pigmentation. Developmentally, she was age appropriate at that first visit. A brain MRI done to evaluate her for tuberous sclerosis revealed multifocal leukoencephalopathy characterized by numerous lesions confined to the hemispheric white matter and T2 hyperintensity observed best on FLAIR sequences, and a corresponding T1 hypointensity. There was no convincing demonstration of subependymal nodules and no gray matter or cortical involvement was identified. Given her brain MRI findings, analysis of very long chain fatty acids for peroxisomal disorders, arylsulfatase A for metachromatic leukodystrophy and galactocerebrosidase for possible Krabbe disease were requested with normal results. She also manifested early development of breasts since the age of 2 years but she did not have any pubic hair, breast discharge, vaginal bleeding or discharge, and had no physical findings consistent with an excessive growth spurt. She was referred to Endocrinology and was given a diagnosis of idiopathic central precocious puberty, after all known etiologies for precocious puberty were ruled out. There was no family history of early onset puberty.

On physical examination, she was in the 25th–50th centile for height (96.1 cm), weight (14.1 kg) and head circumference (47.5 cm). In addition to mild hypertelorism, she had a salmon patch on her forehead and the nape of her neck. Other significant findings were gynecomastia with palpable subareolar tissue and minimal clitoral enlargement. Several telangiectatic patches were also noted in the lower lumbar area and multiple hypopigmented patches were present over her trunk and extremities, many of which were oriented in a

vertical direction (Fig. 1). These were more than 50 in number in a bilateral distribution. Some of them looked like thumb print macules. There were no cafe-au-lait macules.

On subsequent visits, her developmental delay became apparent. At about the age of 6 years, parents reported learning problems, forgetfulness, inattentive and impulsive behaviors and frustration with school. She also had speech/language difficulties as well as fine motor delays. A neuropsychological evaluation diagnosed her as having mild Attention Deficit/Hyperactivity Disorder using Conner's Continuous Performance Test. She demonstrated intellectual abilities within the low average range obtaining a Leiter-R Intelligence Quotient (IQ) of 89 (23rd centile for her age of 6 years and 9 months). At the time of this report, the patient is 8 years of age and attends second grade in regular classes requiring tutoring for mathematics. Her speech has improved significantly after therapy and parents report no additional concerns about her behavior.

MATERIALS AND METHODS

Chromosome analysis of cultured peripheral blood leukocytes as well as skin fibroblasts from the border of the area of hypopigmentation, was carried out using standard protocols. Chromosome microarray analysis (v.6.1) was carried out in peripheral blood leukocytes using a clinically available BAC microarray which includes 1472 BAC and PAC clones. Whole Human Genome Oligo Microarray 244K (Agilent Technologies, Inc., Santa Clara, CA) was used to define the inverted duplicated 13q21 region in cultured fibroblasts. The procedures for DNA digestion, labeling, and hybridization were performed according to the manufacturer's instructions with some modifications [Probst et al., 2007].

RESULTS

G-banded chromosome analysis of cultured peripheral blood leukocytes was initially reported as normal. A skin biopsy was performed on the area of hypopigmentation and chromosomal analysis in cultured fibroblasts revealed an inverted duplicated chromosome 13q21 in 16/20 (85%) cells while the remaining 4/20 cells showed a normal female karyotype (Fig. 2a,b). Repeat analysis of the cultured peripheral blood leukocytes showed the additional inverted chromosome 13q21 to be present in 1 out of 100 cells examined. Fluorescent in situ hybridization studies with whole chromosome 13 paint, confirmed the duplication to be chromosome 13 in origin. Array-CGH using a BAC-microarray on DNA from peripheral blood was reported as normal. High resolution array-CGH using the Agilent 244K oligo array on DNA from skin fibroblasts showed a gain in copy number of chromosome region 13q21-q33 of approximately 48.52 Mb. The 244K array was also performed on DNA sample from a buccal swab which was reported as normal. The 244K array was not performed on peripheral blood.

DISCUSSION

The finding of phylloid hypomelanosis associated with tetrasomy 13q has not been previously reported in the literature. The clinical features present in earlier reported cases of mosaic tetrasomy 13q are mental retardation, hypotonia, bony abnormalities and craniofacial abnormalities (Table I). It is interesting to note that the facial features noted in these three patients outlined in Table I are not similar. One reason could be that the cases reported in the year 2000 were ascertained by G-banding and not by array-CGH. However, given the small sample size, more cases need to be ascertained before we can reach a consensus on the craniofacial abnormalities related with tetrasomy 13q. In addition, the level of mosaicism in different tissues is another variable that could explain the lack of clinical similarity including pigmentation patterns between these cases. Moreover, patients with the same mosaicism

chromosomal abnormality sometimes show a totally different pigmentation pattern [Wertelecki et al., 1986].

There seems to be an increased propensity for neocentromere formation in 13q [Barwell et al., 2004]. To date, 11 cases of inv dup13q neocentromere –containing chromosomes have been reported. The 11 previously reported cases display a wide range of mosaicism, ranging from 100% trisomy for 13q14-qter to 26% hexasomy for 13q32-qter [Li et al., 2002]. An inherent instability of marker chromosomes during early development, perhaps due to slight selection or selective advantage for karyotypically normal cells and/or lack of selection against the marker chromosome is a possible reason for the wide ranging degrees of mosaicism displayed by neocentromere-containing marker chromosomes [Crolla, 1998]. In these 11 patients, no clear genotype–phenotype correlation could be elucidated. Over the years, it has become evident that correlating particular clinical features with specific mosaic chromosomal imbalances is a difficult task exacerbated by the varying degrees of mosaicism that are frequently observed with such chromosomal rearrangements. Furthermore, the presence of a neocentromere in these chromosomes, where the formation of a kinetochore may result in chromatin modification possibly influencing gene expression over a large chromosomal region, may further contribute to the observed clinical heterogeneity.

A total of 76 candidate pigmentary genes have been identified in the genome. Among these genes, three genes are located within the area of duplication found in our patient. *EDNRB* (endothelin receptor type B) maps to 13q22 and functions as a growth factor receptor responsible for melanoblast migration [Sturm et al., 1998]. The other two genes are *DCT* (dopachrome tautomerase) (on 13q32) which functions as a melanosomal enzyme, and *EFNB2* (ephrin-B2) (on 13q33) which is a growth factor also responsible for melanoblast migration [Bouchard et al., 1994; Santiago and Erickson, 2002]. Their role in human disease is not yet known. It is possible that the inverted duplication in our patient caused an overexpression of these genes consequently producing the pigmentary phenotype due to increased gene dosage. Conversely, another possible explanation is that mosaic expression of these genes may lead to impaired melanoblast migration and melanocyte formation leading to the depigmentation.

The developmental delay (including learning disabilities) observed in our patient is also seen in patients with full trisomy 13, although those patients have a worse cognitive outcome. In a review of 8 patients with mosaic trisomy or tetrasomy of 13q, it was found that none of them had holoprosencephaly or other midbrain anomalies, which are hallmarks of full trisomy 13 [Warburton et al., 2000]. These features may be associated with duplication of the most-proximal region of chromosome 13q, which was not observed in our patient. It is possible that gene expression may be inactivated in the vicinity of the neocentromere on these chromosomes, potentially influencing the clinical features in these patients.

The finding of multifocal leukoencephalopathy on her brain MRI could be associated with chromosomal mosaicism in her central nervous system. Her milder cognitive outcome could be due to a potential selection against the inverted duplication in the brain. On the other hand, we are not aware of any reported association with tetrasomy 13q and precocious puberty and it is possible that her precocious puberty could be completely unrelated to the observed chromosomal findings.

In summary, this is a unique association of phylloid hypomelanosis, developmental delay and precocious puberty in an 8-year-old girl with mosaic tetrasomy 13q. It is puzzling that this pattern of phylloid hypomelanosis is observed only with chromosome 13 abnormalities and not with any other mosaic chromosomal abnormalities. Our case further strengthens the

previous evidence that in patients with phylloid hypomelanosis, a chromosomal abnormality involving chromosome 13 needs to be considered.

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FIG. 1. Phylloid pattern of hypopigmentation. Note the leaf like as well as oval thumb print like hypopigmented macules on the front of chest and abdomen; and back. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.].

FIG. 2.

a: Idiogram of chromosome 13 illustrating the inverted duplication. b: G-banding of chromosomes of cultured skin fibroblasts, showing the extra chromosome 13. This was seen in 85% of cells. The rest of the cells had a normal female karyotype.

TABLE I

Comparison of Clinical Features of Our Patient With Patient 13c and 13d [Warburton et al., 2000] With Similar Tetrasomy 13q21-qter

	Our patient	Patient 13c	Patient 13d
Age	8 years	8 years	Died at 13 days
Growth	Normal	Normal	AGA at 7 months
Head	Normal	Normal	Normal CT scan
Facies	Hypertelorism	Submucosal cleft palate and high nasal bridge	Hypertelorism and left cleft lip/gum
Ears	Normal with normal hearing	Conductive deafness and earlobe anomaly	Low set and posteriorly rotated
CNS	Developmental delay particularly speech	Mild mental retardation	Hypotonia
Skin	Salmon patch, phylloid hypomelanosis on back, telangiectatic patches on lower lumbar area	"Patchy pigmentation"	Normal
Heart/lung	Normal	Normal	ASD, VSD, PDA and pulmonary hypoplasia
GI	Normal	Normal	Normal
Extremities	Normal	Right camptodactyly and toe hypoplasia	Left postaxial polydactyly
Skeletal	Normal	Normal	11 ribs and hemivertebrae
Urogenital	Normal female	Normal female	Normal male and renal agenesis
Degree of mosaicism	85%	49%	88%