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A case of constitutional trisomy 3 mosaicism in a teenage patient with mild phenotype

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ABSTRACT

Constitutional mosaicism for trisomy 3 is extremely rare, with only a few postnatally diagnosed cases reported in the literature. We report a case of constitutional trisomy 3 mosaicism in a 16-year-old female, who presented with chronic joint pain, easy bruising, joint hypermobility and dysmorphic features, including long, thin facies, over-folded dysplastic ears, and Pierre-Robin sequence (PRS) with cleft palate. The patient was small at birth, had cleft palate repair, developed chronic joint pain at age 12, and has a history of mild leukopenia and mild thrombocytopenia. Microarray analysis was consistent with a mosaic gain of an entire chromosome 3. FISH analysis of peripheral blood and buccal cells showed the presence of the supernumerary chromosome 3 in a low percentage of cells in both tissues, suggesting that the nondisjunction event occurred prior to the germ cell layer differentiation. Since trisomy 3 has been observed somatically in lymphoma, a Hematology/Oncology consultation was provided for the patient. The oncologist's evaluation for malignancy was unremarkable. A review of findings from other trisomy 3 patients reported in the literature reveals a diverse phenotypic spectrum and does not show a correlation between the proportion of abnormal cells observed in peripheral blood and the patients' clinical features or severity. This case demonstrates that the clinical presentation of an individual with trisomy 3 is highly individualized and the clinical course is difficult to predict.

1. Introduction

Chromosomal aneuploidies occur at an incidence of ~4% in newborns and stillbirths and constitute a major cause of birth defects. Aneuploidies ascertained in the postnatal period most often involve chromosomes 13, 18, 21 and the sex chromosomes (Nagaoka et al., 2012), which encode the fewest genes relative to all other chromosomes (Torres et al., 2008). The rate of aneuploidy in spontaneous abortions is higher, at approximately 35%, with monosomy X and trisomies for chromosomes 15, 16, 21 and 22 being the most commonly observed imbalances (Nagaoka et al., 2012). Changes in the copy number of other autosomes are extremely rare, with relatively few instances reported for each chromosome due to the deleterious effects on the viability of the conceptus (Hassold et al., 1996).

The viability of constitutional trisomies in liveborns is also dependent upon the number and distribution of the trisomic cells in the patient. Trisomies found ubiquitously in all tissues and cells of a patient arise from nondisjunction during meiosis I or meiosis II in the germline and manifest severe phenotypes. Mosaicism for trisomy may arise from one of two mechanisms. Firstly, rescue of an initially trisomic conceptus may occur in a particular cell lineage by extrusion of the third chromosome homolog. Following this event, a concern for uniparental disomy (UPD) emerges with respect to the normal cell line. Secondly, a mitotic nondisjunction error following fertilization may lead to a trisomy in a population of descendent cells and tissues. Patients with mosaicism for a trisomy may be expected to have a milder phenotype than those with trisomy affecting all of their cells.

Here, we describe a rare case of trisomy 3 mosaicism initially

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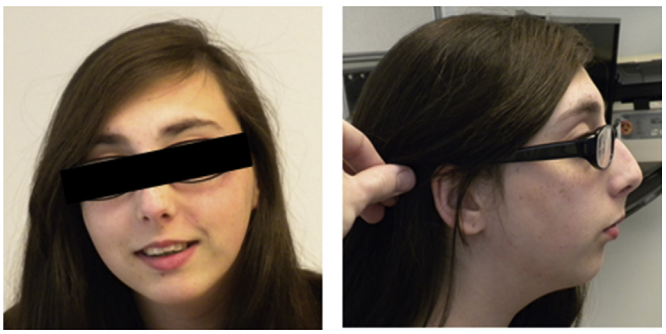

Fig. 1. Patient photographs displaying facial dysmorphic features.

ascertained in a 16-year-old female.

2. Clinical report

Patient: The patient is a 16-year-old female who presented to the Genetics Clinic for dysmorphic features, including long facies, dysplastic ears, prominent eyes, micrognathia and downturned corners of the mouth (Fig. 1). She was born to a 23-year-old mother at 38 weeks gestation by Caesarean section with a birth weight of 2438 g and length of 46.4 cm. She had a history of Pierre Robin sequence (PRS) with cleft palate, deviated septum, a high and convex nasal bridge and hypoplastic alae nasi, asthma, eczema and psoriasis. She had myopia and was prescribed glasses beginning at 7 or 8 years of age. The patient began complaining of joint pain and laxity, affecting her neck, shoulders and knees at the age of 12, though she has never had a joint dislocation or fracture. She bruises easily, develops petechiae upon venipuncture and has exhibited persistent fatigue since age 11. An echocardiogram was normal. She repeated first grade and received speech therapy during preschool. She has a history of mild leukopenia and mild thrombocytopenia. At the time of assessment, at 16 years of age, she attended a mainstream 10th grade classroom and was passing all of her classes. Her growth parameters were as follows: weight 52.9 kg (40th percentile), height 157.9 cm (22nd percentile), occipital frontal circumference 51 cm (<2nd percentile). In addition to dysmorphic features, she was noted to have bilateral flexible flat feet, a Beighton score of 6/9 and a hypernasal voice. The patient's mother has fibromyalgia, chronic joint pain, Hashimoto's thyroiditis, and type 2 diabetes mellitus. There is no family history of arterial aneurysm or dissection, heavy bleeding, pregnancy complications, organ rupture or perforation, or early death. The patient's differential diagnosis included 22q11.2 deletion syndrome, Stickler syndrome and benign joint hypermobility syndrome (hypermobility type Ehlers-Danlos syndrome). Microarray analysis was ordered to investigate for the former.

3. Results

3.1. Microarray analysis

Array comparative genomic hybridization (aCGH) analysis (Agilent GGXChip + SNP v1.0) performed on DNA extracted from peripheral blood showed a pattern consistent with a gain of an

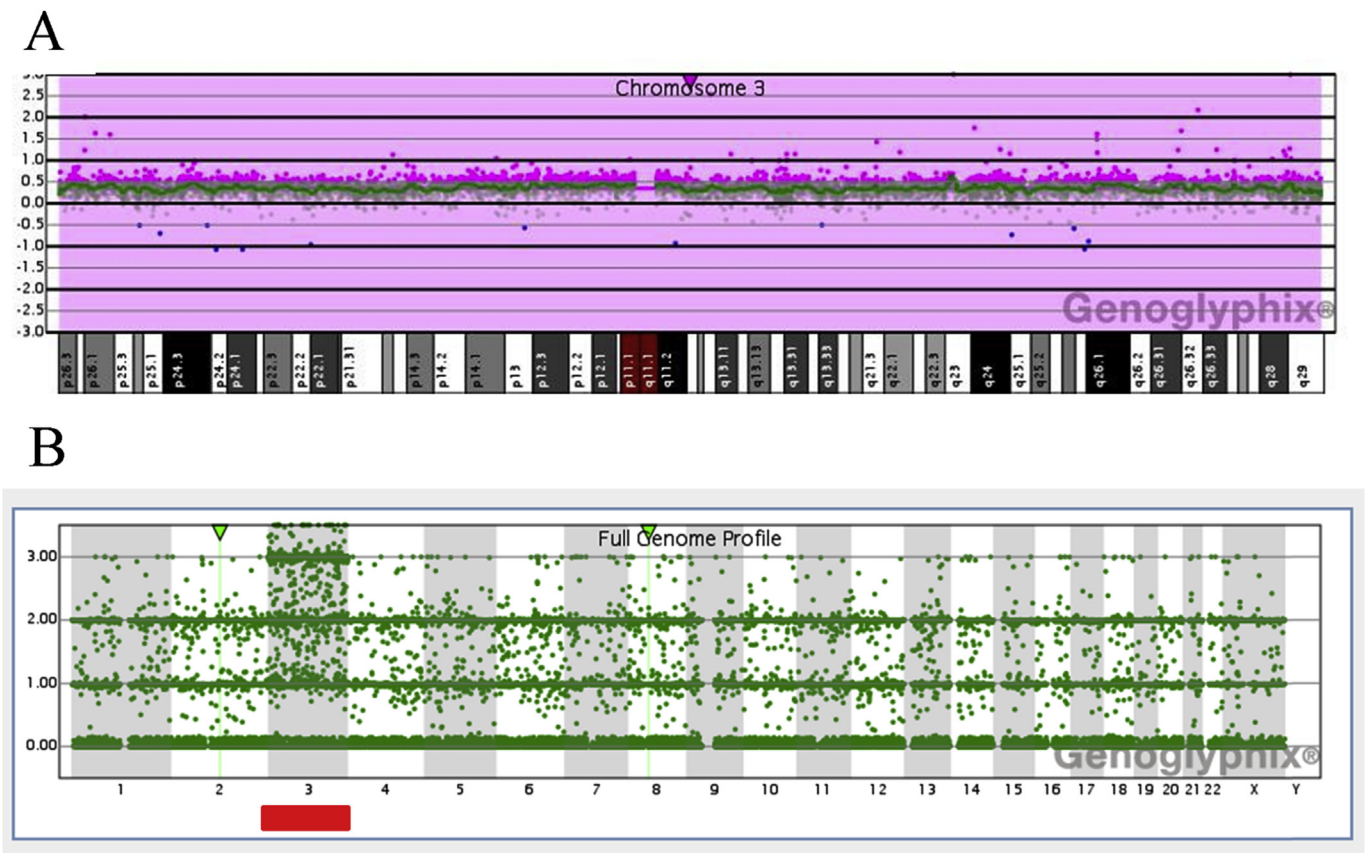

Fig. 2. Microarray analysis showing an increase in dosage of chromosome 3. (A) Genoglyphix profile of chromosome 3 illustrating a copy number gain (pink) of all regions of the chromosome. (B)Genoglyphix whole genome SNP profile demonstrating gains in copy number of SNPs located on chromosome 3 (red bar). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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