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Short clinical report

Blepharophimosis, ptosis, epicanthus inversus syndrome with translocation and deletion at chromosome 3q23 in a black African female

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ABSTRACT

Blepharophimosis–ptosis–epicanthus inversus syndrome (BPES) is a rare autosomal dominant disorder whose main features are the abnormal shape, position and alignment of the eyelids. Type I refers to BPES with female infertility from premature ovarian failure while type II is limited to the ocular features. A causative gene, *FOXL2*, has been localized to 3q23. We report a black female who carried a *de novo* chromosomal translocation and 3.13 Mb deletion at 3q23, 1.2 Mb 5′ to *FOXL2*. This suggests the presence of distant *cis* regulatory elements at the extended *FOXL2* locus. In spite of 21 protein coding genes in the 3.13 Mb deleted segment, the patient had no other malformation and a strictly normal psychomotor development at age 2.5 years. Our observation confirms panethnicity of BPES and adds to the knowledge of the complex *cis* regulation of human *FOXL2* gene expression.

1. Introduction

Blepharophimosis–ptosis–epicanthus inversus syndrome (BPES) is a rare autosomal dominant disorder. About one hundred cases are reported in various publications. About half of the cases are familial and may be transmitted over several generations, while other cases are sporadic [1]. Ocular abnormalities include blepharophimosis, ptosis, telecanthus, and epicanthus inversus [1]. BPES has been divided into two types [2]. In type I, eye abnormalities are associated with female infertility due to ovarian failure with early menopause [3,4]; in type II, only eyelid abnormalities are observed. A causative gene has been localized at 3q23 [5,6]. Mutations in the *FOXL2* gene at 3q23 have been reported in both BPES types [7–9]. Approximately 50% of cases result from *de novo* mutations. A small fraction of cases did not show *FOXL2* mutations but were associated with chromosomal abnormalities in the 3q23 region with evidence for an altered regulation of *FOXL2* expression leading to BPES [10,11]. *FOXL2* is involved in ovarian development, and has been shown to play a major role in granulosa cell tumors, a rare type of ovarian cancer [12]. Better knowledge of the *cis* factors that regulate *FOXL2* gene expression has thus important implications for BPES patients and for granulosa cell tumor patients, as well as for ovarian development and premature ovarian failure in general. Because of the large fraction of cases resulting from new mutations, BPES is expected to be panethnic. In this paper, we report on a black African female who presented with eye anomalies and was diagnosed with a BPES associated with a chromosomal translocation and deletion at 3q23, upstream of *FOXL2*.

2. Case report

A 3-month old girl, was referred to the genetics clinic for facial dysmorphism noticed at birth. She was the first daughter of non consanguineous Beninese parents and was born at term after a normal pregnancy. In particular, a fetal sonogram was normal. Delivery was unremarkable. Birth weight, height and head circumference were respectively 3.100 kg (M), 51 cm (M) and 35 cm (M). Family history was unremarkable. Physical examination at age of 3 months showed facial dysmorphism with telecanthus, blepharophimosis, upslanting palpebral fissures, flat nasal bridge and a relative macrostomia (Fig. 1). An umbilical hernia was present. Psychomotor development was normal with good head control, adequate intentional smile and normal audition and vision. At age two years and a half, no harmful event had occurred. The

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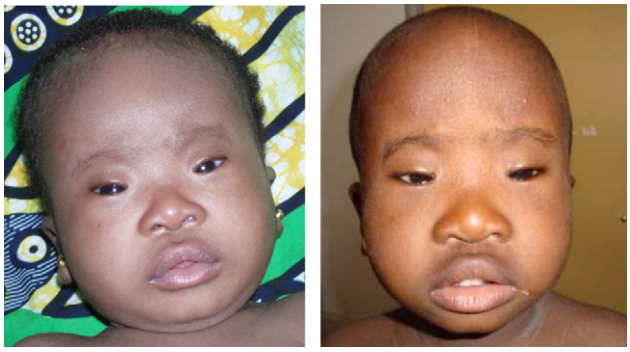

Fig. 1. Facial dysmorphism with telecanthus, blepharophimosis, upslanting palpebral fissures, flat nasal bridge and a relative macrostomia (at 3 and 12 months).

psychomotor development was strictly normal, even ahead of milestones according to the World Health Organization's motor development windows' achievement [13]. Indeed, the child sat, crawled, stood and walked at respectively five, six, eight and ten months. She was clean by day and night at 30 months. She also showed good communication abilities and brilliant mental performances. Ultrasonographic studies of the heart, kidneys and brain showed no anomaly. Thorough examination of both parents showed no blepharophimosis, no inverse epicanthus, nor ptosis. A conventional karyotype performed on cultured lymphocytes at 550 G-band resolution revealed an apparently balanced translocation [*t*(1; 3)] (Fig. 2). This finding was confirmed on fluorescence in situ hybridization (FISH) analysis using whole chromosomes 1 and 3 painting probes (Fig. 3). A microarray comparative genomic hybridization was performed, which disclosed a deletion of ~3.13 Mb at chromosome 3q23 (genomic coordinates 139 933 444–143 032 502, hg 19) (Fig. 4). The parents' chromosomes were normal on conventional karyotyping, FISH analysis and microarray comparative genomic hybridization, showing that this translocation occurred *de novo*. Our patient's phenotype was typical of BPES and the molecular cytogenetics findings were consistent, since the 3q23 deletion was located in the vicinity of *FOXL2*, 1.2 Mb upstream of the *FOXL2* gene transcription unit.

3. Discussion

Here we report a patient with a blepharophimosis ptosis and epicanthus inversus syndrome, with no sign of psychomotor impairment. Our patient showed all the symptoms of this condition according to the list of characteristics reported in the complete syndrome [1]. There were no other cases in the family, consistent with a fresh occurrence of the disorder, although in spite of thorough examinations some cases show variable expressivity [14]. Considering the important facial dysmorphism at birth, a chromosomal analysis was performed. The standard karyotype analysis showed a chromosomal translocation with some doubt about a possible deletion. FISH analysis with whole chromosome painting then showed a simple reciprocal translocation. Array-CGH identified an interstitial deletion at the 3q23 translocation breakpoint. The *de novo* (1; 3) translocation occurring in our patient is associated with a deletion in 3q23 encompassing 3.13 Mb which contains 21 protein-coding genes. We could assume that this deletion acts on basal *FOXL2* expression through a position effect as it is located 1.2 Mb in the 5′ region of the gene (telomeric). Position effects have already been described through long-range *cis*-acting regulatory elements located more than 1 Mb upstream of the ORF [15]. Alternatively to a position effect, deletions occurring 250 Kb telomeric, i.e. 5′ to *FOXL2* have been described as removing putative transcription-factor binding sites of *FOXL2* [11]. An apparently balanced *de novo* translocation at 3q23 was recently reported in a girl with BPES, where CGH revealed a small chromosomal deletion, telomeric (5′) to *FOXL2* and centromeric to the presently reported deletion [16]. Our patient's deletion seems to be the most distant deletion ever described in BPES, suggesting that this gene has numerous and far distant regulatory elements. Moreover, bioinformatic tools, like UCSC Regulation tracks from ENCODE project, showed many potential regulatory elements in the deleted region that could act on *FOXL2* expression. The tracks called H3K4Me1 and H3K27Ac show where modification of histone proteins is

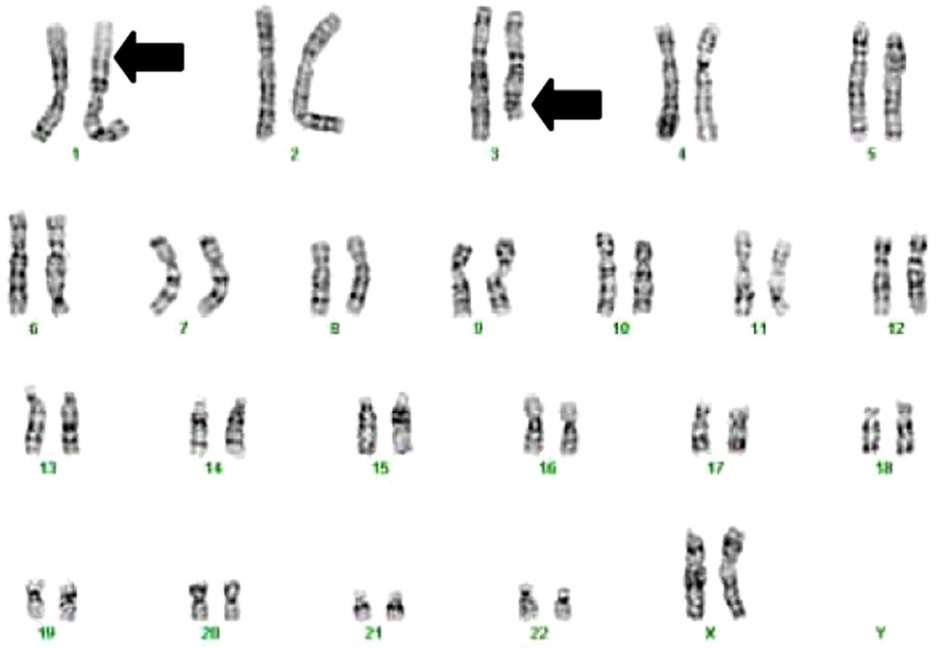

Fig. 2. Conventional karyotype with material exchange between chromosomes 1 and 3 (black arrows show the break and fixing points).