Blepharophimosis-Ptosis-Epicanthus Inversus Syndrome in a Girl with Chromosome Translocation t(2;3)(q33;q23)

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Online Publication Date: 01 March 2008

To cite this Article Tzschach, Andreas, Kelbova, Christina, Weidensee, Sabine, Peters, Hartmut, Ropers, Hans-Hilger, Ullmann, Reinhard, Erdogan, Fikret, Jurkatis, Jan, Menzel, Corinna, Kalscheuer, Vera and Demuth, Stephanie(2008)'Blepharophimosis-Ptosis-Epicanthus Inversus Syndrome in a Girl with Chromosome Translocation t(2;3)(q33;q23)', Ophthalmic Genetics, 29:1, 37 — 40

To link to this Article DOI: 10.1080/13816810701867615
URL: http://dx.doi.org/10.1080/13816810701867615
CASE REPORT

Blepharophimosis-Ptosis-Epicanthus Inversus Syndrome in a Girl with Chromosome Translocation t(2;3)(q33;q23)

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We report on a young female patient with the clinical features of blepharophimosis-p toesis-epicanthus inversus syndrome (BPES, OMIM 110100) and a balanced chromosome translocation 46,XX,t(2;3)(q33;q23)dn. BPES is a rare autosomal dominant congenital disorder characterized by the eponymous ocular-facial features that are, in female patients, associated either with (type 1 BPES) or without (type 2 BPES) premature ovarian failure. Both types of BPES are caused by heterozygous mutations in the FOXL2 gene, which is located in chromosome band 3q23. Chromosome aberrations such as balanced rearrangements have only rarely been observed in BPES patients but can provide valuable information about regulatory regions of FOXL2. The translocation in this patient broadens our knowledge of pathogenic mechanisms in BPES and highlights the importance of conventional cytogenetic investigations in patients with negative results of FOXL2 mutation screening as a prerequisite for optimal management and genetic counseling.

Keywords  FOXL2; balanced chromosome translocation; blepharophimosis-p toesis-epicanthus inversus syndrome; BPES; premature ovarian failure

INTRODUCTION

Blepharophimosis-p toesis-epicanthus inversus syndrome (BPES, OMIM 110100) is a rare autosomal dominant congenital disorder characterized by short palpebral fissures, epicanthus inversus, ptosis of the eyelids and additional ocular and non-ocular features.1 In female patients, BPES can be associated with premature ovarian failure (POF), menstrual irregularities or infertility (type 1 BPES); or it is not associated with fertility problems (type 2 BPES).2,3 In the majority of patients, BPES is caused by heterozygous mutations of the FOXL2 gene which encodes a forkhead transcription factor that is expressed in the developing eyelid and ovaries4,5 BPES is rarely associated with chromosome aberrations such as deletions or rearrangements,6,7 and an autosomal
recessive form of BPES associated with a homozygous FOXL2 mutation has recently been reported in a consanguineous Indian family.8

Here, we report a young BPES patient in whom FOXL2 mutation analysis failed to identify a mutation, but subsequent chromosome analysis revealed a de novo balanced chromosome translocation involving the FOXL2 locus.

CLINICAL REPORT

The patient was born to healthy and non-consanguineous parents after an uneventful pregnancy in the 37th gestational week. Birth parameters were within the normal range [length 47 cm (50th centile); weight 3365 g (50th centile); head circumference 32 cm (10th centile)]. Psychomotor development was normal. On examination at the age of 14 months, her height was 75 cm (25th centile) and head circumference 46 cm (25–50th centile). Facial dysmorphic features included short palpebral fissures (blepharophimosis) and lateral displacement of inner canthi (telecanthus), bilateral ptosis of eyelids, bilateral epicanthus inversus, sparse eyebrows, long philtrum, flat nasal bridge and anteverted nares (Figure 1A). Ophthalmologic investigations revealed no abnormalities of the eye or the retina. The clinical features were strongly suggestive of blepharophimosis- ptosis-epicanthus inversus syndrome.

MATERIAL AND METHODS

FOXL2 Mutation Analysis

For FOXL2 mutation analysis we used the primers as reported in Crisponi et al. (2001).4 Details of the PCR and sequencing conditions are available upon request.

Karyotyping, Array CGH and FISH

Cytogenetic investigations (GTG banding) on 25 metaphases obtained from PHA-stimulated peripheral lymphocytes were performed according to standard protocols.

Array comparative genomic hybridisation (array CGH) analysis was performed on a “32k” BAC array as described previously.9 Aberrations were only considered if at least three adjacent clones were involved unless they coincided with published DNA copy number variants as listed in the Database of Genomic Variants (http://projects.tcag.ca/variation/). Detailed step-by-step protocols are provided on our website (http://www.molgen.mpg.de/~abt_rop/ molecular_cytogenetics/).

For fluorescence in situ hybridization (FISH) experiments, a permanent lymphoblastoid cell line of the patient was established by EBV transformation according to standard protocols after informed consent. FISH was performed using three BAC clones (RP11-809A16; RP11-186B11; RP11-34M23) at and around the FOXL2 locus in 3q32. The BAC clones were selected from the Human “32k” BAC Re-Array set (http://bacpac.chori.org/pHumanMinSet.htm; kindly provided by Pieter de Jong, Children’s Hospital Oakland Research Institute). DNA samples were prepared according to standard protocols and were labelled by nick translation with either biotin-16-dUTP or digoxigenin-11-dUTP. Immunocytochemical detection of probes was performed as described elsewhere.10 Chromosomes were counterstained with 46-diamino-2-phenyl-indole (DAPI). Metaphases were analysed with a Zeiss epifluorescence microscope.

RESULTS

No Mutation in FOXL2

Sequencing of FOXL2 failed to detect pathogenic mutations.

A Chromosome Breakpoint Affects the FOXL2 Locus

Chromosome analysis in the patient revealed a balanced reciprocal translocation between one homologue of chromosome 2 and one homologue of chromosome 3 in all metaphases.
The presence of a chromosome rearrangement in a patient with a monogenic disorder illustrates the importance of conventional cytogenetic analyses in situations where molecular genetic tests of the respective genes are available, but re-sequencing of these genes fails to identify causative mutations. In BPES patients, molecular and/or cytogenetic confirmation of the clinical diagnosis is important not only to exclude other disorders associated with blepharophimosis [e.g., Michels syndrome (OMIM 257920), Ohdo syndrome (OMIM 249620), Marden-Walker syndrome (OMIM 248700), Dubowitz syndrome (OMIM 223370) or the syndrome reported by Khan et al.], but also because female patients can be at risk to develop premature ovarian failure or other fertility problems (BPES type 1). Firm establishment of the diagnosis in childhood provides the rationale for pre-symptomatic tests of ovarian function, early therapeutic intervention (e.g., hormone replacement therapy, ovarian tissue cryopreservation) and/or counseling for reproductive choices (e.g. to plan pregnancies earlier rather than later in life). Knowledge of a balanced chromosome rearrangement is even more important for those patients who are able to procreate, since the formation of germ cells with unbalanced chromosome complements can lead to reduced fertility rates, higher risks for abortions and increased risks for the birth of disabled children with unbalanced chromosome aberrations.

In summary, the unusual chromosome disorder of this patient adds to our understanding of the pathogenesis of BPES and highlights the importance of conventional cytogenetic investigations in patients with negative results in FOXL2 mutation screening as a prerequisite for optimal management and genetic counseling.

ACKNOWLEDGMENTS
We thank the parents of the patient for their support and Hannelore Madle and Susanne Freier for technical assistance. We gratefully acknowledge support from the German National Genome Research Network (NGFN, project numbers 01GR0105 and 01GR0144).

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