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Original article

Blepharophimosis and mental retardation (BMR) phenotypes caused by chromosomal rearrangements: Description in a boy with partial trisomy 10q and monosomy 4q and review of the literature

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Abstract

Blepharophimosis is a rare congenital anomaly of the palpebral fissure which is often associated with mental retardation and additional malformations. We report on a boy with blepharophimosis, ptosis and severe mental retardation carrying an unbalanced 4;10 translocation with terminal duplication of 10q [dup(10)(q25.1→qter)] and monosomy of a small terminal segment of chromosome 4q [del(4)(34.3→qter)]. Detailed clinical examination and review of the literature showed that the phenotype of the patient was mainly determined by the dup(10q). This paper reviews the chromosomal aberrations associated with BMR (blepharophimosis mental retardation) phenotypes. Searching different databases and reviewing the literature revealed 14 microscopically visible aberrations (among them UPD(14)pat) and two submicroscopic rearrangements causing blepharophimosis and mental retardation (BMR) syndrome. Some of these

Abbreviations: BMR, blepharophimosis and mental retardation; Array-CGH, array comparative genomic hybridization; UPD, uniparental disomy.

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rearrangements—like the terminal dup(10q) identified in our patient or interstitial del(2q)—are associated with clearly defined phenotypes and can be well distinguished from each other on basis of clinical examination. This paper should assist clinicians and cytogeneticists when evaluating patients with BMR syndrome.

Keywords: Blepharophimosis; Chromosomal aberration; Mental retardation; Monosomy 4q; Palpebral fissures; trisomy 10q

1. Introduction

Blepharophimosis is defined as a reduction of both the horizontal and vertical dimension of the palpebral fissure. It is usually associated with other periocular abnormalities such as ptosis, telecanthus and epicanthic folds [11]. Blepharophimosis can either occur as an isolated feature in otherwise healthy individuals, or in combination with additional features in a number of congenital syndromes. In the latter it often constitutes an important diagnostic feature [5]. Examples include monogenetic syndromes such as the BPES (blepharophimosis, ptosis, epicanthus inversus syndrome, OMIM 110100) and the Freeman Sheldon syndrome (OMIM 193700), as well as genetic syndromes of yet unknown aetiology such as Ohdo and Ohdo-like syndrome (OMIM 249620) [6,21,32].

In the majority of individuals with syndromic blepharophimosis, however, no specific diagnosis can be established. These patients usually show variable degrees of mental retardation, and blepharophimosis occurs in combination with additional malformations other than of the periocular region. These patients are diagnosed as BMR (blepharophimosis mental retardation) syndrome, a term describing a phenotypically and aetiologically heterogeneous group of patients [32]. It is very likely that the majority of patients with such unclassified BMR phenotypes carry chromosomal aberrations, although the underlying rearrangements can not always be detected by conventional chromosomal analysis.

Here we report on a boy who presented with pronounced blepharophimosis, ptosis, hypotonia and developmental delay and was diagnosed as BMR syndrome. Cytogenetic analysis, including array-CGH (comparative genomic hybridization), revealed an unbalanced 4;10 translocation with terminal duplication of 10q encompassing the segment 10q25.1→qter, and monosomy of the terminal segment of chromosome 4q (4q34.3→qter).

A thorough review of the literature on chromosomal aberrations associated with BMR phenotypes revealed that dup(10q) constitutes one of the best characterized chromosomal rearrangements causing this syndrome [23]. Further clearly defined entities—mainly caused by large deletions or duplications—could be identified, as for example interstitial del(2q) and terminal dup(6p). Interestingly, submicroscopic rearrangements such as the recently identified microdeletions on 17q [del(17)(q21.31)] and 8q [del(8)(q22.1)] also cause BMR phenotypes [15,24,25]. Since even large chromosomal rearrangements are not always easy to detect in standard chromosome preparations, it is recommended, therefore, to apply FISH techniques using subtelomeric probes and/or array-CGH to evaluate unclassified BMR phenotypes.

2. Case report

The boy was born after an uneventful pregnancy at $38^{5}/_{7}$ weeks of gestation to a 31-year-old mother and a 37-year-old father of Sri Lankan descent. He was the product of