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Short report

Subtelomeric trisomy 21q: A new benign chromosomal variant

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Abstract

The diagnosis of a subtelomeric rearrangement has immediate impact on counseling, particularly in the case of familial rearrangements. However, the existence of subtelomeric imbalances with absent phenotypic effects may hamper genetic counseling, particularly when the rearrangement has not been previously described. We report on a new subtelomeric polymorphism, consisting of a familial subtelomeric rearrangement of chromosome 19 resulting in distal trisomy for 21q, detected in a child with Angelman Syndrome (AS) due to an UBE3A mutation.

This report shows that new, previously unknown, benign subtelomeric variants may complicate the correct clinical diagnosis.

Keywords: Benign subtelomeric variant; 21q trisomy; Translocation; UBE3A

1. Introduction

For the past decade, the list of new molecular cytogenetic methods with potential applications in diagnosis and prognosis of mental retardation (MR) and/or multiple congenital

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anomalies (MCA) has been increasing, thanks to the use of different new methods (FISH, molecular genotyping, array-CGH). However, the success rate in identifying cryptic chromosome imbalances in subjects with apparently normal karyotype depends on many factors, including clinical indications, medical and family history, degree of clinical urgency, accessibility to technical approaches [23].

It is well known that ''hidden'' rearrangements involving the subtelomeric regions can be missed in routine karyotype analysis at 550-band level. The subtelomeric regions of human chromosomes are known to be gene rich [18], to have the highest recombination rate and to be prone to aberrations resulting from illegitimate pairing and cross-over [14]. Consequently, different strategies have been developed to investigate their role in genetic disorders [5,12,17].

Initial surveys on subjects with malformations and mental retardation gave an overall frequency of subtelomeric imbalances of approximately 5–6 % with a range of 2–29% due to different inclusion criteria [3]. The detection rate, recently reported by Ravnan et al. [15] in a study population on 11,688 cases referred for subtelomeric FISH testing, was approximately 2.5%, with an additional 0.5% of presumed familial variants.

Interpreting subtelomeric imbalances can be complicated by the fact that, in addition to those telomeric rearrangements that are most likely causative of the phenotype (deletions 1p, 22q, 4p, 9q, 8p, 2q and 20p), there are also deletions or duplications of the subtelomere regions that appear to be benign variants because the imbalance is subsequently detected in one healthy parent [8,15].

We describe a subject with Angelman syndrome, caused by a point mutation in UBE3A, and a subtelomeric chromosome rearrangement consisting on trisomy 21q owing to transposition on chromosome 19q. The same rearrangement was present in the father. We characterized the rearrangement by FISH and performed whole genome array-CGH analysis in order to calibrate the impact of this cryptic chromosome aberration on the patient's phenotypic abnormalities.

2. Case report

The proband is a 3-year-old female, the second child of healthy unrelated parents, and meets the diagnostic criteria for AS: severe learning disability, epileptic seizures, ataxia, absent speech, and dysmorphic facial features. The skull was asymmetric with plagiocephaly, the face showed high frontal region, arched eyebrows, deep-set eyes, low-set ears, thick lips and microcephaly.

After the exclusion of deletion of 15q11-13, pUPD15 and MECP2 mutations, the analysis for UBE3A mutations resulted positive.

However, the clinical picture was not informative for AS in the first months of life of the patient, so a subtelomeric test was performed. FISH-subtelomeric analysis revealed a 21q translocation owing to a transposition on 19q. The same cryptic chromosome rearrangement was detected in the healthy father and grandfather.

3. Materials and methods

Routine cytogenetic analysis (400–550 band) was performed on proband, parents' and grandparents' blood using standard high-resolution techniques [6].

The TelVysion kit with telomere specific probes was used according to the supplier's instructions (Vysis Inc, Downers Grove, IL). Fluorescent in situ hybridization (FISH) to chromosome preparations from the patient, her father and grandfather was done with Bacterial