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Short report

Concurrent transposition of distal 6p and 20q to the 22q telomere: A recurrent benign chromosomal variant

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Abstract

We report the second instance of a complex unbalanced rearrangement consisting of distal trisomy 6p and 20q due to the concurrent transposition of distal 6p and 20q to the 22q telomere, previously described as a benign familial chromosomal variant. In the previous case, the nonpathogenicity of the rearrangement was based on the absence of genotypic differences between the affected proband and his normal father, and on the absence of imprinted genes in the unbalanced region. We now describe the same variant in an unrelated affected subject, in whom testing confirmed the diagnosis of Angelman syndrome, and in his healthy father. Molecular investigations confirmed that the two families have an identical subtelomeric rearrangement. However, genotyping of the flanking sequences on 22q showed a completely different pattern in the two families, demonstrating that they are indeed unrelated. Array-CGH analysis with a resolution of ~20 kb (Kit 244A, Agilent) defined a deletion size of 5.9 Mb on 15q11.2. No other imbalances were visible at subtelomeric regions.

Further Array-CGH analysis using DNA of the proband (as test) and his mother (as reference) did not detect any duplication at the 6p and 20q subtelomeric regions. The proband and his father appear to have

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a copy number of the transposed regions equal to that of individuals with a normal repartition of the subtelomeric regions. This is not suggestive of a trisomy but rather of CNV regions. This type of rearrangement could define a new class of polymorphic variants, i.e. positional variants, as observed for pericentromeric heterochromatin.

Keywords: Recurrent benign subtelomeric variant; Polymorphic variants; Angelman syndrome; CNV

1. Introduction

Direct transmission of a chromosome imbalance from parent to child provides the opportunity of discerning whether the imbalance is pathogenic or a benign variant. Barber [1] in a recent review reported on 130 directly transmitted cytogenetically visible unbalanced chromosome rearrangements. In 30/130 cases, phenotypically abnormal children had the same imbalance as an unaffected parent, and in a further 23/130 cases phenotypically normal probands and parents had the same imbalance. In recent years, FISH analysis performed to test subtelomeric integrity has allowed the identification of subtelomeric rearrangements in ~5% of subjects with MR, with a range of 2–29% due to different inclusion criteria [15]. A number of subtelomeric imbalances with no apparent phenotypic effects have been reported [2,11,13,14,17,4,5]. Recently, in a study of 11,688 unselected patients referred for subtelomeric FISH, the frequency of subtelomeric rearrangements was of 2.5%, with 0.5% of cryptic imbalances identified as familial variants [15] because they were also present in phenotypically normal parents. Consequently, the identification of subtelomeric variants requires both clinical genetic precision, to exclude subtle phenotypic manifestations in apparently normal individuals, and laboratory resources, to distinguish clinically silent variations from pathogenic rearrangements [6].

We have previously hypothesised that a subtelomeric rearrangement consisting of distal trisomy 6p and 20q due to the concurrent transposition of distal 6p and 20q to the 22q telomere could be a genomic polymorphism, because it was present in the proband and in his healthy father [3]. Here, we report on an unrelated subject with confirmed Angelman syndrome who also carries a familial subtelomeric rearrangement, identical at BAC/PAC level to the one we previously described.

2. Case report

The proband was a 12-month-old boy, the first child of non-consanguineous Caucasian parents. He was investigated for moderate global developmental delay and acquired microcephaly, with his head circumference having fallen from the 50th centile at birth to the 2nd centile at the time of assessment. He was hypotonic and hypopigmented, with a fair complexion, blond hair and blue eyes. He had a wide mouth and pointed chin and was brachycephalic. Examination was otherwise normal. Although the diagnosis of Angelman syndrome was suspected at that stage, the proband's mother was pregnant at the time of review and a number of investigations were done simultaneously to give the best chance of making a diagnosis which would allow accurate genetic counseling in relation to the pregnancy. Investigations included FISH for a deletion of 15q11.2, using the D15S10 probe (Vysis), which confirmed the diagnosis. However,