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Clinical report

Constitutional chromoanasynthesis: description of a rare chromosomal event in a patient

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ABSTRACT

Structural alterations in chromosomes are a frequent cause of cancers and congenital diseases. Recently, the phenomenon of chromosome crisis, consisting of a set of tens to hundreds of clustered genomic rearrangements, localized in one or a few chromosomes, was described in cancer cells under the term chromothripsis. Better knowledge and recognition of this catastrophic chromosome event has brought to light two distinct entities, chromothripsis and chromoanasynthesis. The complexity of these rearrangements and the original descriptions in tumor cells initially led to the thought that it was an acquired anomaly. In fact, a few patients have been reported with constitutional chromothripsis or chromoanasynthesis. Using microarray we identified a very complex chromosomal rearrangement in a patient who had a cytogenetically visible rearrangement of chromosome 18. The rearrangement contained more than 15 breakpoints localized on a single chromosome. Our patient displayed intellectual disability, behavioral troubles and craniofacial dysmorphism. Interestingly, the succession of duplications and triplications identified in our patient was not clustered on a single chromosomal region but spread over the entire chromosome 18. In the light of this new spectrum of chromosomal rearrangements, this report outlines the main features of these catastrophic events and discusses the underlying mechanism of the complex chromosomal rearrangement identified in our patient, which is strongly evocative of a chromoanasynthesis.

1. Introduction

Structural alterations in chromosomes have long been implicated both in developmental anomalies and cancers. These chromosomal aberrations are termed "complex" when the rearrangement involves more than two breakpoints [Zhang et al., 2009]. They classically arise from DNA double-strand breaks, which can happen in either the germline or the somatic cells.

Recently, using SNP array and next-generation paired-end sequencing across a range of tumor cell types, Stephens et al. [2011] highlighted a striking copy number profile in these cells, consisting of a set of tens to hundreds of clustered genomic rearrangements, localized on one or a few chromosomes. They described for the first time a very complex chromosomal rearrangement, resembling chromosome pulverization, which they named chromothripsis, literally "chromo" for chromosome and "thripsis" for shattering into pieces. Astoundingly, this phenomenon was found to be relatively common in tumors, accounting for 2–3% of all cancer samples and up to 25% of primary bone cancers. Stephens et al. [2011] argued that this phenomenon occurred in a single cellular catastrophe and could promote the cancerisation of these cells.

Although the causes and underlying mechanism of these events still remain unclear, many studies have implicated the DNA repair machinery in these rearrangements and in particular, the non-homologous end joined (NHEJ) mechanism [Chen et al., 2012; Stephens et al., 2011]. Taking into consideration the characteristics of the NHEJ repair system, we can imagine a stressful situation where multiple DNA double-strand breaks appear simultaneously in a single chromosomal region. The chromosome region would thereby be shattered into pieces, with most pieces having blunt

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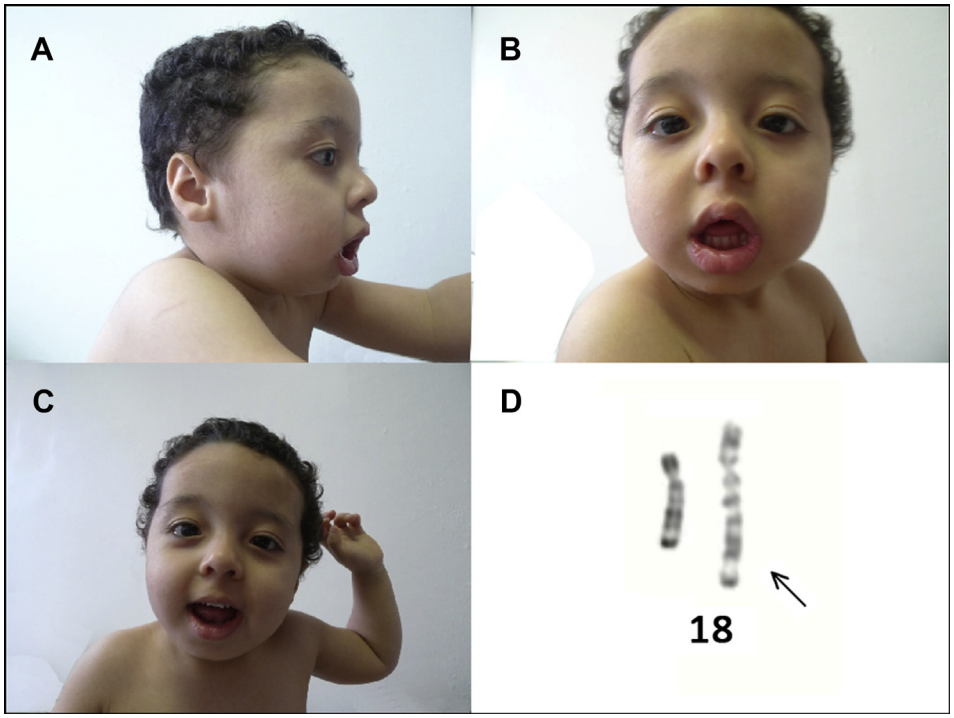

Fig. 1. **A, B, C**: Photographs of the proband at the age of 30 months. Note the round hypotonic face, the telecanthus with the downslanted palpebral fissures and the low and posteriorly rotated ears, and **D**: RHG-banding showing complex rearrangement of one of the copies of chromosome 18 of the patient (the derivative chromosome is marked by an arrow).

junctions. While some pieces are lost (which could thus form double-minute chromosomes), the retained fragments could then be randomly put together by the NHEJ repair system. This would explain the presence of deletions, insertions and inversions as well as translocations when more than one chromosome is affected by the phenomenon [Stephens et al., 2011]. Copy neutral chromothripsis has also been described [Kloosterman et al., 2012]. However, this model does not fully explain duplications or triplications occurring within the rearranged chromosome. This last profile with extra copies suggests the intervention of replicative processes like fork-stalling and template switching (FoSTes) [Lee et al., 2007] and the microhomology mediated break-induced replication (MMBIR) system [Hastings et al., 2009]. The MMBIR appears to be a good candidate [Chen et al., 2012; Liu et al., 2011]. Indeed, this system is a low-processivity replicative system, using serial template switching and microhomology regions to repair, providing an explanation for both the microhomology sequence at the breakpoint junctions and the insertions of short segments flanked by microhomology around the junctions [Liu et al., 2011]. The term chromoanasynthesis was proposed to illustrate this second mechanism, literally “chromo” for chromosome and “anasynthesis” for reconstitution [Liu et al., 2011].

Such chromosomal crisis events are now quite well known in cancer [Boeva et al., 2013; Kloosterman et al., 2011; Magrangeas et al., 2011; Mehine et al., 2013; Molenaar et al., 2012; Rausch et al., 2012] but far less so in developmental diseases [Chiang et al., 2012; Kloosterman et al., 2011, 2012; Liu et al., 2011; Nazaryan et al., 2013]. Here we describe a child with a syndromic intellectual disability who has a highly complex genomic rearrangement, strongly evocative of chromoanasynthesis.

2. Clinical report

The proband is a 30 month old boy. He is the only child of young unrelated parents, both of Arabic origin, with no personal or family history of intellectual disability, behavioral difficulties or malformations. There were no miscarriages in the maternal obstetric history. The patient was born in Morocco at term after an uneventful pregnancy. His weight and length were normal for the gestational age but the head circumference was at +3 SD. The neonatal period was complicated by tracheomalacia and feeding difficulties that resolved spontaneously after a few months of life. He was first referred for neuropediatric examination because of global developmental delay. He walked at 26 months of age and said only a few words by 30 months of age. Neurological examination was normal. He was noted to be hyperactive. His medical examination at the age of 30 months in the clinical genetics department revealed facial dysmorphism (a round hypotonic face, telecanthus with downslanted palpebral fissures and mildly dysplastic ears which were low and posteriorly rotated) (Fig. 1). He had no limb abnormalities. At the age of 30 months, his growth was normal for all parameters and his head circumference was within the normal range (−0,5 SD). Auditory tests revealed normal hearing and ophthalmologic examination was also normal. No other malformations were found. No specific diagnosis could be given at the time of the initial genetics consultation.

This study was approved by our institutional ethics committee and blood samples were obtained from the proband and his mother, after informed consent from the mother. No blood sample was available from the father. Karyotype analysis in the patient showed an abnormal chromosome 18 with a complex rearrangement (Fig. 1). Karyotype analysis of the mother was normal.

In order to further characterize this structural aberration, we used an SNP-array (whole genome Affymetrix microarray, CytoscanHD) (Affymetrix, Santa Clara, CA, USA) with a resolution of 40 Kb. The complex chromosome rearrangement, confined to chromosome 18, consisted of seven duplicated segments of the long arm of chromosome 18 and one triplicated segment of the short arm (Fig. 2). The size of these regions ranged from 200 Kb to 5 Mb, representing around 20 Mb of surplus chromosomal material. The chromosomal