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ScienceDirect
European Journal of Medical Genetics 51 (2008) 219–225
EUROPEAN JOURNAL OF MEDICAL GENETICS
http://www.elsevier.com/locate/ejmg

Short report

A complex submicroscopic chromosomal imbalance in 19p13.11 with one microduplication and two microtriplications

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Received 18 October 2007; accepted 28 December 2007
Available online 9 January 2008

Abstract

Complex chromosomal rearrangements [CCRs] are considered very rare, but are being detected with an increasing frequency because of the enhanced resolution of novel molecular karyotyping techniques like array-CGH. This report describes a patient carrying a unique CCR involving one duplication and two triplications in a 3.2 Mb region on 19p13.11. The patient presented with microcephaly, velopharyngeal insufficiency, dysmorphism, mental retardation and a muscular ventricular septal defect. We show that CCRs are likely to be more frequent than hitherto appreciated. This has important consequences for genotype–phenotype correlations and warrants caution before labelling imbalances as ''simple''.

Keywords: Array-CGH; Complex intrachromosomal rearrangement; 19p13.11; Duplication; Triplication; Ventricular septal defect; Microcephaly; Mental retardation

1. Introduction

Several definitions exist for the term 'Complex chromosomal rearrangements' [CCRs]. In this study we consider chromosomal rearrangements as complex if they involve three or

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doi:10.1016/j.ejmg.2007.12.009

more chromosomes or four or more breakpoints [8,15]. These CCRs have long been considered rare, found only in a minute subset of patients that carry chromosomal imbalances [2]. Aberrant G-banding patterns are still attributed to simple deletions or duplications. The exact nature and extent of an imbalance is often not studied in detail, using an independent technique such as FISH, or is often done by testing only one or a few loci. Given the laborious nature of these investigations, very few aberrations were thus mapped with a high resolution. Only when multiple chromosomes were visibly aberrant, it was evident that multiple chromosomal breaks were present in one patient. This might explain why most reported CCRs detected by classical karyotyping are interchromosomal (affecting multiple chromosomes) [2].

Recently, however, a novel technique for genome-wide copy number assessment was developed, array comparative genomic hybridisation [array-CGH] [12,13]. It has been implemented as a routine molecular karyotyping technique, and reports have shown it is a valuable tool in the diagnosis of patients with mental retardation [MR] [11,14]. Identification of chromosomal imbalances using array-CGH infers a precise delineation of all boundaries of the imbalances. As a consequence, an increased amount of CCRs are being detected using this technique [4–6,15,17,18,20]. Similarly, also interchromosomal rearrangements are often found to be more complex upon closer examination [3,7]. We describe here a CCR of chromosome 19p13.11 that involves a duplication and two triplications.

2. Clinical description

This girl was born as the second child of healthy, non-consanguineous parents. Family history is negative with regard to mental handicap and congenital malformations. Pregnancy was complicated by placental abruption. She was born at a gestational age of 37 weeks. Birth weight and length were not available. She was diagnosed at birth with multiple small ventricular septal defects (VSD) and a large midmuscular VSD. Aged 2.5 years she underwent a surgical correction of strabismus. Carbamazepine was started at the age of four years because of myoclonic seizures. Brain MRI was normal. At the age of five she was enlisted in special education for severe psychomotor delay, scoring an IQ of 52 on the SON-R non-verbal intelligence test. Clinical examination at age 11 showed a biometry with all parameters below the third centile (weight = 22.8 kg, length = 124 cm, head circumference = 50 cm). There was facial dysmorphism with a broad nasal bridge, a thin upper lip, mild retrognathia and bilateral ptosis. She had long fingers, talipes valgus and a sacral dimple.

3. Material and methods

Routine karyotyping at ISCN 550+ was performed on G-banded metaphase spreads from PHA-stimulated peripheral lymphocytes. Array-CGH was performed as described previously [11]. Two different micro-arrays were used: one contained 3600 BAC/PAC clones obtained from the Sanger institute with a genome-wide coverage providing a 1 megabase [Mb] resolution, a second contained 709 BAC/PAC clones that were obtained from BACPAC Resources Children's Hospital, Oakland, USA that provide a tiling-path coverage of chromosome 19. Micro-array construction [10], FISH [11], short tandem repeat [STR] analysis [16] and real-time quantitative PCR [qPCR] analysis [11] were performed as described in the references. Oligonucleotide primers used in this study are described in Tables 1 and 2. Coordinates for genomic locations mentioned in this study are according to NCBI genome build 36.