Meta Gene 2 (2014) 799–806

Contents lists available at ScienceDirect

Meta Gene

19q13.33→qter trisomy in a girl with intellectual impairment and seizures

Gianna Carvalheira [a], Mariana Moysés Oliveira [a], Sylvia Takeno [a], Fernanda Teresa de Lima [b], Vera Ayres Meloni [a], Maria Isabel Melaragno [a,*]

[a] Universidade Federal de São Paulo — UNIFESP, Department of Morphology and Genetics, São Paulo, Brazil
[b] Universidade Federal de São Paulo — UNIFESP, Department of Mastology, São Paulo, Brazil

ARTICLE INFO

Article history:
Received 14 July 2014
Revised 1 September 2014
Accepted 8 September 2014
Available online 27 October 2014

Keywords:
Translocation t(19q;21p)
de novo 19q13.33 trisomy
Gene regulation
Intellectual impairment
Seizures

ABSTRACT

Rearrangements in chromosome 19 are rare. Among the 35 patients with partial 19q trisomy described, only six have a breakpoint defined by array. The 19q duplication results in a variable phenotype, including dysmorphisms, intellectual disability and seizure. In a female patient, although G-banding at 550 band-resolution was normal, multiplex ligation-dependent probe amplification (MLPA) technique and genomic array showed a 10.6 Mb terminal duplication of chromosome 19q13. Fluorescent *in situ* hybridization (FISH) revealed that the duplicated region was attached to the short arm of chromosome 21 and silver staining showed four small acrocentrics with nucleolar organization region (NOR) activity, suggesting that the breakpoint in chromosome 21 was at p13. This is the first *de novo* translocation between 19q13.33 and 21p13 described in liveborn. The chromosome 19 is known to be rich in coding and non-coding regions, and chromosomal rearrangements involving this chromosome are very harmful. Furthermore, the 19q13.33→qter region is dense in pseudogenes and microRNAs, which are potent regulators of gene expression. The trisomic level of this region may contribute to deregulation of global gene expression, and consequently, may lead to abnormal development on the carriers of these rearrangements.

Introduction

Developmental delay and intellectual disability affect around 3% of the general population (Shevell et al., 2003). In many cases, although patients present normal karyotypes, they can be carriers of cryptic genomic

* Corresponding author.
E-mail address: melaragno.maria@unifesp.br (M.I. Melaragno)

http://dx.doi.org/10.1016/j.mgene.2014.09.004

imbalances which, when detected, are important for both accurate diagnosis and genetic counseling. Rearrangements involving chromosome 19, either duplications or deletions, have rarely been reported. The main clinical features in partial 19q trisomy include low birth weight, short stature, abnormal ears, short neck, intellectual disability and seizures (Dorn et al., 2001; Lenzini et al., 2010). Seven patients with pure 19q trisomy, and 28 patients with other concomitant chromosome imbalances, have been published. We describe a female patient, carrier of a *de novo* terminal 19q trisomy, the first case of translocation between 19q and 21p in liveborn. The extra 19q region contains a high density coding and non-coding DNA sequences, including both pseudogenes and microRNAs, which have a critical role in gene expression control. The deregulation of transcript levels due to the chromosomal rearrangement may lead to abnormal development and other clinical features. Here, three specific genes and the possible roles of regulatory elements, at trisomic level, in the 19q region will be discussed, as well as the relationship between phenotype and possible molecular mechanisms involved in the clinical characteristics of the patient.

Patient and methods

Clinical report

The patient described here, an only child of a young healthy and consanguineous couple, presents with mild dysmorphic features and intellectual disability (Table 1). The female patient was born at term by vaginal delivery, with a weight of 2900 g (50th centile), and unreported length and head circumference. At eight days old, she was hospitalized with a urinary tract infection. Until the age of four years, she had other urinary tract infections, bronchopneumonia episodes, urolithiasis and anemia. She evolved with moderate neuromotor developmental and speech delay, and non-quantified intellectual disability. At the age of four years she started to have seizures, which have been controlled by valproic acid and levomepromazine treatment to date. She is now aged 12 years. Upon genetic evaluation, at eight years and 10 months of age, her measurements were: height 112 cm (<3rd centile), weight 23 kg (10th–25th centile), and head circumference 51 cm (50th centile). Her main dysmorphic features were (Supplementary data, Fig. S1): short stature; ocular hypertelorism; downturned corners of mouth; posteriorly rotated ears; prominent antihelix; short neck; short, cold and congested hands and fingers; clinodactyly of the 5th fingers; and thoracolumbar scoliosis. Because of the congested hands she was referred to a rheumatologist for evaluation, which was normal.

Cytogenetic and molecular analysis

Chromosomal analysis with 550 resolution G-banding was performed on lymphocyte cultures from the patient and her parents, based on a total of 20 metaphase cells. Genomic DNA from whole blood was isolated using the Gentra Puregene Kit (Qiagen-Sciences, Germantown, USA). MLPA (multiplex ligation-dependent probe amplification) technique, using the SALSA MLPA P070 Human Telomere-5 kit (MRC-Holland, Amsterdam, The Netherlands), that contains probes for subtelomeric regions, was performed to verify possible cryptic genome imbalances. Genomic array was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix Inc., Santa Clara, CA, USA), and the data were analyzed with the Genotyping Console 3.0.2 and Chromosome Analysis Suite (ChAS) software (Affymetrix) based on GRCh37/hg 19. To validate the results from MLPA and array assays, and to investigate the trisomic segment localization, fluorescent *in situ* hybridization (FISH) on metaphase spreads was performed using a BAC probe for 19q13.43 (RP11-359B7). Silver staining was performed to verify the nucleolus organizer region (NOR) activity, using 50% silver nitrate in formic acid water.

Results

G-banding karyotypes of the patient (Supplementary data, Fig. S2A) and her parents were normal. Due to phenotypic features present in the patient, MLPA was performed and revealed three copies of the subtelomeric 19q region with probe *BC-2*, localized in 19q13.43 (Supplementary data, Fig. S2B and S2C). Genomic array showed a 10.6 Mb triplication of 19q as follows: arr19q13.33q13.43(48,463,121-59,097,842)×3 (Fig. 1A). Since the array technique does not allow the determination of the extra segment position, FISH with a 19q13.43 BAC probe (RP11-359B7) revealed that it was attached to the short arm of one chromosome 21 in the