Gene Reports 4 (2016) 218–221

Contents lists available at ScienceDirect

Gene Reports

journal homepage: www.elsevier.com/locate/genrep

16p13.3 microduplication syndrome: A new characteristic case without intellectual disability

Chiara Palka [a], Melissa Alfonsi [b,*], Elisena Morizio [c], Paolo Guanciali-Franchi [b,c], Angelika Mohn [a], Francesco Chiarelli [a], Giandomenico Palka [b,c], Giuseppe Calabrese [c]

[a] Department of Pediatrics, "G. d'Annunzio" University, Chieti, Italy
[b] Department of Medical Genetics, "SS Annunziata" Hospital, Chieti, Italy
[c] Department of Oral Sciences, Nano and Biotechnologies, "G. d'Annunzio" University, Chieti, Italy

ARTICLE INFO

Article history:
Received 5 April 2016
Received in revised form 20 June 2016
Accepted 4 July 2016
Available online 7 July 2016

Keywords:
Array-CGH
Intellectual disability
Facial dysmorphisms
CREBBP
Microduplication
Rubinstein–Taybi

ABSTRACT

Interstitial 16p13.3 microduplication, encompassing the *CREBBP* gene, is now considered a well recognizable syndrome. To date, 28 patients have been reported with a 16p13.3 microduplication. The majority of the patients share a similar phenotype which is mainly characterized by typical facial dysmorphisms and variable intellectual disability. Other features include microcephaly, growth retardation, limb anomalies and defects of the brain, heart, genitalia, palate and eyes.

We report on a *de novo* microduplication of chromosome 16p13.3 revealed using array-comparative genomic hybridization (array-CGH) technology in a patient presenting with variable congenital anomalies and typical facial dysmorphisms, but with no evidence of developmental delay.

This case highlights the importance of an accurate clinical examination and the utility of array-CGH in pediatric patients with a characteristic phenotype but without intellectual disability.

1. Introduction

Interstitial 16p13.3 microduplication, encompassing the *CREBBP* gene, is now considered a well recognizable syndrome, which is complementary to the deletion found in severe Rubinstein–Taybi syndrome (RTS), caused by a microdeletion of the same chromosomal region (Thienpont et al., 2010). To date, 28 patients have been reported with a 16p13.3 microduplication ranging from 0.24 Mb to 3.5 Mb in size. Despite this difference in extent of microduplication, the critical duplicated region contains a single gene: *CREBBP*, which is considered the major gene of the 16p13.3 microduplication syndrome; furthermore, the majority of the patients share a similar phenotype, which is mainly characterized by typical facial dysmorphisms and variable intellectual disability (ID) (Friedman et al., 2006; Thienpont et al., 2007; Marangi et al., 2008; Dallapiccola et al., 2009; Mattina et al., 2012; Chen et al., 2012; Tüysüz et al., 2012; Li et al., 2013; Demeer et al., 2013). Other features are microcephaly, growth retardation, limb anomalies and defects of the brain, heart, genitalia, palate and eyes. Most of the reported cases present a 16p13.3 microduplication that has occurred *de novo*, with the exception of 2 cases who inherited the aberration from an apparently normal parent (Thienpont et al., 2010). However, the frequent *de novo* occurrence and the low frequency in patients with developmental delay or congenital defects (0.043–0.069%) indicate that this microduplication is associated with a reduced reproductive fitness (Thienpont et al., 2010; Cooper et al., 2014).

Here we describe a *de novo* 1.28 Mb microduplication of 16p13.3 chromosome, identified by array-CGH, in a female patient with multiple congenital anomalies and facial dysmorphisms but no evidence of developmental delay.

2. Case report

The patient is an 18-month-old female, the second child of non-consanguineous, healthy parents. Family history is unremarkable. Delivery was performed at 38 gestational weeks, after an uneventful pregnancy. Birth length was 50 cm (25–50th centile), weight 3.470 kg (25–50th centile) and head circumference 34 cm (25-50th centile). At birth, multiple anomalies were noticed. She presented a schisis of the soft palate which was surgically corrected at once, right talo-valgus foot which was corrected with manipulation. An echocardiography was performed and revealed a heart defect characterized by inter-atrial and inter-ventricular septal defects, which were spontaneously closed.

Her clinical features at the time of our evaluation showed normal anthropometric measurements. Psychomotor development results

Abbreviations: RTS, Rubinstein–Taybi syndrome; ID, intellectual disability; IUGR, intrauterin growth retardation.

* Corresponding author at: Department of Medical Genetics, "SS Annunziata" Hospital, Via dei Vestini, 15, 66100 Chieti, Italy.
E-mail address: melissa.alfonsi@gmail.com (M. Alfonsi).

http://dx.doi.org/10.1016/j.genrep.2016.07.001
2452-0144/

correct for her age: the girl started speech at 8 months and walking at 12 months. Facial dysmorphisms were observed. In particular, round face and short neck, hypertelorism with upslanting palpebral fissures, bilateral epichantus, bulbous nose, low-set ears, molar hypoplasia and micrognathia. Furthermore, she presented telethelia and small hands and feet with broad thumb and hallux.

The G-banded karyotype on cultured lymphocytes of the proband has been interpreted to be normal 46,XX. On the basis of the presence of multiple congenital anomalies and dysmorphisms, we performed an array-comparative genomic hybridization (array-CGH) analysis using the CytoChip 575-kb resolution BAC array (BlueGnome, Cambridge, UK), according to the recommendations of the manufacturer. Data were analyzed using the Blue-Fuse for microarrays software package (BlueGnome). The analysis identified a microduplication of 1.28 Mb on chromosome 16p13.3, bridging from clone RP11-361I19, at position 3,386,121 bp, to clone RP11-89M4, at position 4,670,238 bp, according to the human genome NCBI Build 37 version (Fig. 1a). The duplicated segment included approximately 4 known genes, among which *CREBBP* deletions or mutations have been correlated with RTS (Fig. 1b). Thus, the chromosomal abnormality was confirmed by fluorescence *in situ* hybridization (FISH) analysis using a commercially available probe for the *CREBBP* region according to the manufacturer's instructions.

The parent's karyotype and FISH analysis were normal.

3. Discussion

In this study, we report the description of an 18-month-old patient with a *de novo* 1.28 Mb 16p13.3 microduplication, encompassing 4 known genes. The *GLIS2* gene has been correlated with recessive nephronophthisis, *SLX4* with recessive Fanconi anemia, *DNASE1* with susceptibility to Systemic Lupus Erythematosus and the *CREBBP* gene (Fig. 1b). Mutations and deletions of *CREBBP* have been reported in patient affected by RTS and is the major gene involved in the microduplication syndrome of the same region (Thienpont et al., 2007; Hennekam, 2006).

It is known that each human has an individual combination of CG-CNVs (cytogenetically visible copy number variation) and MG-CNV (molecular genetics copy number variation). These regions can include heterochromatine which is are typically gene-poor and even euchromatine which contain genes. Most of MG-CMV are considered as benign and are usually inherited from a parent. On the contrary, if they are determined as *de novo* genomic imbalances and if contain genes MG-CMV are considered more likely pathological (Liehr, 2016).

To date, 16p13.3 region has not been reported as a variant. Moreover, the presence of OMIM genes and the absence of this anomaly in the parents come out in favour of the pathological role of it.

16p13.3 microduplication syndrome is known to be mainly characterized by mild to moderate ID, characteristic facial dysmorphisms and occasionally defects of the brain, heart, limb, genitalia, palate and eyes (Thienpont et al., 2010; Marangi et al., 2008).

To better understand the phenotypic details, we compared the clinical data of the 28 previously reported patients and our patient (Fig. 2, Table 1). The data supports the hypothesis that developmental milestones delay and/or ID are the major characteristics, being observed in approximately 90% of cases. In fact, these features have been observed in all patients except 3, all too young to be evaluated (2 patients described by Demeer et al., 2013 and the present case). Distinct facial dysmorphisms are shared by many patients such as upslanting palpebral fissures (75%), narrow palpebral fissures (57%), hyperthelorism (57%), wide nasal bridge (64%), bulbous nasal tip (71%), long philtrum (50%), low set ears (53%). Other previously reported features such as sparse and fine hair (29%), high forehead (46%), ptosis (45%), epicanthus (39%), low nasal bridge (39%), small nares (39%), thickened lips (48%), micrognathia (32%) and short/webbed neck (32%), are less frequent but can be observed. Behavioural problems and anomalies of the extremities (proximally implanted thumbs and camptodactyly)

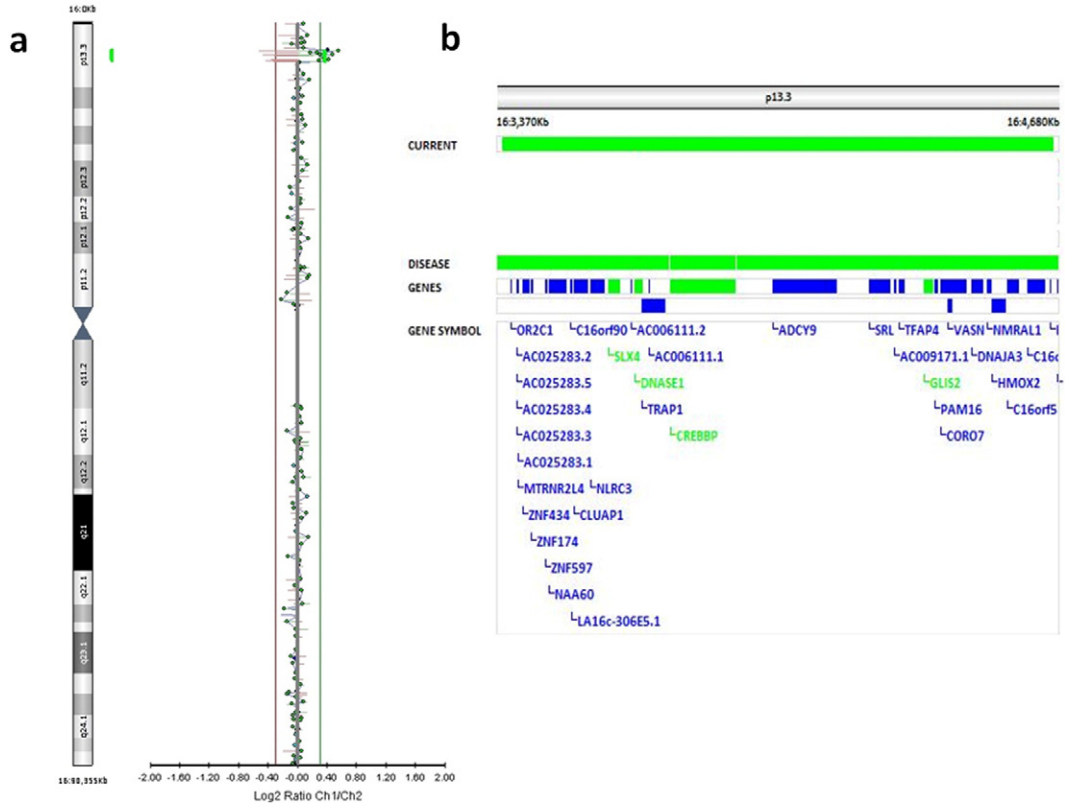

Fig. 1. a) Array-CGH analysis: the 16p13.3 microduplication is represented by a green line; b) schematic representation of the 16p13.3 microduplication (green line) and the genes involved in the aberration (green words).