European Journal of Medical Genetics 55 (2012) 747–752

Contents lists available at SciVerse ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Short clinical report

Interstitial 16p13.3 microduplication: Case report and critical review of genotype–phenotype correlation

Teresa Mattina [a,1], Orazio Palumbo [b,2], Raffaella Stallone [b,2], Rita Maria Pulvirenti [c], Laura Di Dio [d], Piero Pavone [e], Massimo Carella [b,*,2], Lorenzo Pavone [f]

[a] Medical Genetics University of Catania, Department of Pediatrics Building 4, Via Santa Sofia 78, 95123 Catania, Italy
[b] Casa Sollievo della Sofferenza Hospital, IRCCS, San Giovanni Rotondo, Italy
[c] Department of Pediatrics Building 2, Via Santa Sofia 78, 95123 Catania, Italy
[d] Dottorato di Ricerca in Malattie Genetiche dell'Età Evolutiva, Medical Genetics University of Catania Building 4, Via Santa Sofia 78, 95123 Catania, Italy
[e] Azienda Ospedaliera Universitaria Policlinico-OVE, Via Santa Sofia 78, 95123 Catania, Italy
[f] Pediatrics University of Catania, Azienda Ospedaliera Universitaria Policlinico-OVE, Via Santa Sofia 78, 95123 Catania, Italy

ARTICLE INFO

Article history:
Received 11 May 2012
Accepted 15 September 2012
Available online 29 September 2012

Keywords:
CREBBP
16p13.3 microduplication
SNP array analysis
Smallest region of overlap

ABSTRACT

We report on a patient with a recognizable phenotype of intellectual disability, multiple congenital anomalies, musculoskeletal anomalies and craniofacial dysmorphisms, carrying a *de novo* 0.4 Mb duplication of chromosome region 16p13.3 detected by SNP-array analysis. In addition, myopia, microcephaly and growth retardation were observed. The causal 16p13.3 duplication is one of the smallest reported so far, and includes the CREB binding protein gene (*CREBBP*, MIM 600140), whose haploinsufficiency is responsible for the Rubinstein–Taybi syndrome, and the adenylate cyclase 9 gene (*ADCY9*, MIM 603302). By comparing the clinical manifestations of our patient with those of patients carrying similar rearrangements, we confirmed that 16p13.3 microduplications of the Rubinstein–Taybi region result in a recognizable clinical condition that likely represents a single gene disorder. In addition, our case allowed us to define with more precision the smallest region of overlap (SRO) in all patients reported so far, encompassing only the *CREBBP* gene, and is useful to confirm and further define the phenotypic characteristics due to duplication of the *CREBBP* gene, being the first case of interstitial duplication with microcephaly and growth defects reported to date.

1. Introduction

Rubinstein–Taybi syndrome (RTS) is a 16p13.3 haploinsufficiency condition caused by microdeletion (10%) or loss-of-function mutations (45%) of CREB binding protein (*CREBBP*) gene [4]. 16p13 microduplication in the Rubinstein–Taybi region is an emerging syndrome recently described, characterized by a consistent phenotype [3,7]. Clinical features include congenital anomalies, typical facial characteristics, moderate developmental delay with intellectual disability and limb anomalies. In this paper, we describe a new case with recognizable phenotype of multiple congenital abnormalities, dysmorphic features and intellectual disability in which a *de novo* 0.4 Mb duplication of chromosome region 16p13.3 was detected by SNP-array analysis. At clinical evaluation, he also showed growth retardation. Moreover, we present a genotype–phenotype correlation and comparison with patients, carriers of similar duplications in size and genomic localization, from the literature.

2. Case report

An 11-year-old male was admitted to our facility for evaluation of facial dysmorphism, short stature, mental and motor delay. There was no relevant family history. He was first in birth order, of non-consanguineous parents with a normal younger brother. Pregnancy was complicated by oligohydramnios. The mother denied substance use during pregnancy. He was born at term but was small for gestational age with: weight 2300 g, (−2 SD); height 46 cm,

Abbreviations: RTS, Rubinstein–Taybi syndrome; *CREBBP*, cAMP-response elements binding protein; *ADCY9*, adenylate cyclase 9; ASD, atrial septal defect; VSD, ventricular septal defect; SRO, smallest region of overlap.

* Corresponding author. Medical Genetics Unit, IRCCS Casa Sollievo della Sofferenza, 71013 San Giovanni Rotondo (FG), Italy. Tel.: +39 0882 416350; fax: +39 0882 411616.
E-mail addresses: mattina@unict.it, mattina@hotmail.it (T. Mattina), o.palumbo@operapadrepio.it (O. Palumbo), raffaella.stallone@gmail.it (R. Stallone), ritula76@hotmail.it (R.M. Pulvirenti), lauradidio@libero.it (L. Di Dio), ppavone@unict.it (P. Pavone), m.carella@operapadrepio.it (M. Carella), LPavone@unict.it (L. Pavone).
[1] Tel./fax: +39 095 3782450.
[2] Tel.: +39 0882 416350; fax: +39 0882 41161.

1769-7212/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmg.2012.09.006

(−2 SD); head circumference 31 cm, (<−2 SD). He had respiratory distress at birth with APGAR scores of 6 and 7 at 1 and 5 min. He underwent an inguinal herniorrhaphy at age 1 year. The patient's psychomotor and mental delay was recognized since his 1st year of life. At 18 months, he was unable to stand up or speak; he walked independently at age 2 years. At age 11 his weight was 24.2 kg (<−3 SD), height 133.5 cm (<−1 SD), and head circumference 49 cm (<−3 SD).

Clinical evaluation showed microcephaly, low frontal hair line, upslanting and narrow palpebral fissures with bilateral ptosis, epicanthus, hypertelorism, dyschromia of the irides, myopia, a broad nasal bridge, thickened lips, a "v" shaped mouth with down-turned corners, small crowed teeth, small ear lobes, auricular prominence more evident on the right, micrognathia, high arched and narrow palate, sialorrhoea. His hands were small and broad with short and proximally implanted thumbs, mild skin syndactyly and 5th finger clinodactyly, and camptodactyly of the 1st, 3rd, 4th and 5th fingers of the left hand, and 2nd, 4th and 5th fingers of the right hand. His feet were small with metatarsus varus and short and stubby first toes (Fig. 1). He had a thoracic deformity, dorsal hyperkyphosis, lumbar hyperlordosis, scoliosis, stiff elbows and knees. His genitalia were characterized by shawl scrotum and hypospadias, for which he underwent three surgical corrections. Neurologic examination showed developmental delay but a good response to his environment. Evaluation of cognitive functioning showed moderate to severe mental delay (WISC-R: QIV 44, QIP 38, QIT 34). Skeletal radiographs, including skull x-rays, showed normal bone age and confirmed microcephaly and other anomalies including: square thorax, long and narrow pelvis and cleft of the posterior arch of the first sacral vertebra, asymmetrical femurs with a wide angle of femur inclination on the right, cone shaped third phalanges of the 1st and 2nd fingers, deformity of 2nd phalanges of the 5th fingers, and short first metatarsal bones and cone shaped distal phalanges of the 1st toes. Echocardiography showed mitral valve hyperechogenity, and mitral valve prolapse with mild to moderate insufficiency. Abdominal ultrasound showed ectopic and

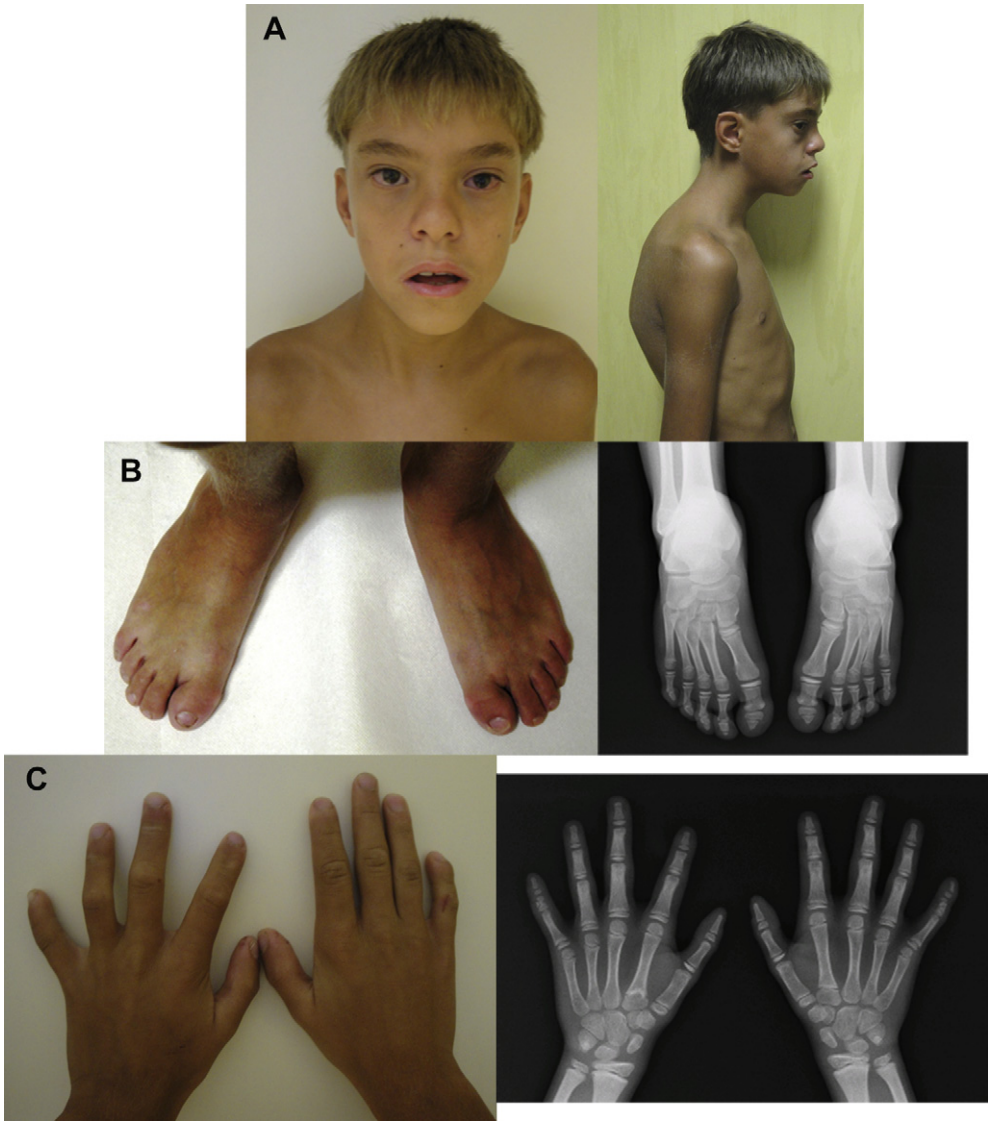

Fig. 1. A: Face with upward slant of palpebral features, narrow palpebral fissures, palpebral ptosis and epicanthus, dysmorphic ears, thoracic deformity; B: Feet with short and stubby first toes, X-rays showing short first metatarsal bones and cone shaped distal phalanges of the 1st toes; C: Hands with low set thumbs, mild skin syndactyly, 5th finger clinodactyly, camptodactyly of the 1st, 3rd, 4th and 5th fingers of the left hand, and 2nd, 4th and 5th fingers of the right hand, X-rays showing cone shaped third phalanges of the 1st and 2nd fingers.