European Journal of Medical Genetics 55 (2012) 238–244

Contents lists available at SciVerse ScienceDirect

European Journal of Medical Genetics

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

Original article

Interstitial deletion of chromosome 2p15-16.1: Report of two patients and critical review of current genotype–phenotype correlation

Maria Piccione [a,*], Ettore Piro [a,1], Francesca Serraino [a,1], Simona Cavani [b,2], Roberto Ciccone [c,3], Michela Malacarne [b,2], Mauro Pierluigi [b,2], Marianna Vitaloni [c,3], Orsetta Zuffardi [c,3], Giovanni Corsello [a,4]

[a] U.O. Pediatria e TIN Dipartimento Materno-Infantile, Università degli Studi di Palermo via Alfonso Giordano 3, 90127 Palermo, Italy
[b] Laboratorio di Genetica, E.O. Galliera, Via A. Volta 6, Genova 16128, Italy
[c] Patologia Umana ed Ereditaria. Sez Biologia e Genetica, Università degli Studi di Pavia, Via Forlanini 14 27100, Italy

ARTICLE INFO

Article history:
Received 4 April 2011
Accepted 30 January 2012
Available online 18 February 2012

Keywords:
Array CGH
Developmental delay
Dysmorphic features
Microdeletion 2p15p16.1 syndrome

ABSTRACT

We report two individuals with developmental delay and dysmorphic features, in whom array-based comparative genomic hybridization (array CGH) led to the identification of a 2p15p16.1 *de novo* deletion. In the first patient (Patient 1) a familial deletion of 6q12, inherited from her father, was also detected. In the second patient (Patient 2) in addition to the 2p15p16.1 microdeletion a *de novo* deletion in Xq28 was detected. Both individuals shared dysmorphic features and developmental delay with the six reported patients with a 2p15p16.1 microdeletion described in medical literature. Conclusion: in the first patient a 642 kb 2p16.1 deletion (from 60.604 to 61.246 Mb), and a 930 kb 6q12 familial deletion, was detected and in the second a 2.5 Mb 2p15p16.1 deletion (from 60.258 to 62.763 Mb), with a Xq28 deletion, was discovered. The common dysmorphic features and neurodevelopmental delay found in these patients are in agreement with the clinical phenotype of a microdeletion syndrome involving 2p15p16.1. Our data confirm the hypothesis suggesting that 2p15p16.1 deletion is a contiguous gene syndrome.

1. Introduction

Intellectual disability (ID) and behavioral problems can be caused by cryptic chromosome abnormalities including subtelomeric rearrangements. Conventional karyotyping is often unable to identify submicroscopic chromosomal changes. The advent of new technologies, like array-based comparative genomic hybridization (array CGH), has increased the number of microdeletions and microduplications associated with phenotypic features, frequently including idiopathic intellectual disability (ID) [1]. New high resolution genetic analysis techniques often provide an explanation or a diagnosis of abnormal conditions and help us to find a more precise characterization of genotype/phenotype correlation in childhood chromosomal anomalies.

Up to now seven patients with del(2)(p15p16.1) have been identified by array CGH [2–7]. They presented with intellectual disability and dysmorphic facial features such as shortened palpebral fissures, widened inner canthal distance, epicanthal folds, large ears and broad and high nasal root and tip. Autism spectrum disorders have been also described in patients with del(2)(p15p16.1) [8]. Here we describe two individuals with ID and dysmorphic features, in whom the array CGH led to the identification of a *de novo* deletion of 2p15p16.1.

2. Clinical description

2.1. Patient 1

Patient 1 is a 2-year-old female, second child of unrelated healthy Italian parents (mother 38 years old, father 49 years old), born by cesarean section after 38 weeks of gestation. Apgar scores were 7 and 8 at 1 and 5 min respectively. Weight was 4100 g (90th centile), length 51 cm (50th centile) and head circumference 34.5 cm (5th centile). Dysmorphic features consisted of flat facial profile,

* Corresponding author. Tel.: +39 916555440; fax: +39 916555429.
E-mail addresses: piccionemaria@libero.it (M. Piccione), ettore.piro@unipa.it (E. Piro), fraserraino@hotmail.com (F. Serraino), simona.cavani@galliera.it (S. Cavani), roberto.ciccone@unipv.it (R. Ciccone), michela.malacarne@galliera.it (M. Malacarne), mauro.pierluigi@galliera.it (M. Pierluigi), marianna.vitaloni@unipv.it (M. Vitaloni), zuffardi@unipv.it (O. Zuffardi), giocors@aliceposta.it (G. Corsello).
[1] Tel.: +39 91 6555456.
[2] Tel.: +39 10 5634375.
[3] Tel.: +39 382 987733.
[4] Tel.: +39 91 6555425.

1769-7212/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmg.2012.01.014

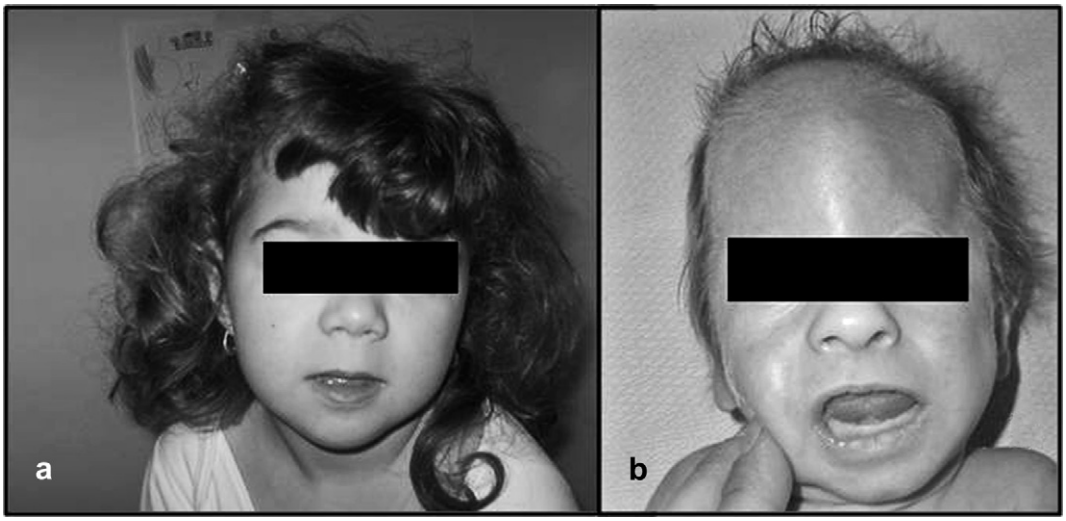

Fig. 1. (a) Clinical features of patient 1. Flat facial profile, thin upper lip (b) Clinical features of patient 2: trigonocephaly with ridging of the metopic suture, severe bitemporal narrowing with elongated face, low set and posteriorly rotated ears, macrostomia.

convergent strabismus, downslanting palpebral fissures, inner canthal distance of 3.5 cm (>97 th centile), epicanthal folds, depressed nasal root, long philtrum, thin upper lip (Fig. 1A). She also showed hypoplasia of the labia minora. Mental development index score on the Bayley II Scale (MDI) was 52, in the range of severely delayed performance with mixed receptive-expressive language delay. Psychomotor development index on the Bayley II Scale (PDI) was 79, in the range of mild delayed performance; neurological examination showed a mild generalized hypotonia of central origin. She developed mild microcephaly (45.8 cm), in contrast with normal length and weight growth velocities. A brain MRI was normal. Cardiologic evaluation including electrocardiogram and echocardiography and abdominal ultrasound investigations were normal. Brainstem Auditory Evoked Response (BAER) and Flash Visual Evoked Potentials (FVEP) were within normal limits.

At the age of 4 years Childhood Autism Rating Scale (CARS) [9] did not reveal autistic features. The child behavior profile, assessed by Child Behavior Checklist for Ages 1.5–5 (Achenbach T. 2000 ASEBA University of Vermont) [10] showed the presence of mild externalizing behavior problems with attention deficit and aggressiveness. The child was defined by her parents as defiant, disobedient and uncooperative.

2.2. Patient 2

Patient 2 is a 4-month-old male, first child of unrelated healthy Italian parents (mother 28 years old, father 33 years old), with intrauterine growth restriction (IUGR) and a prenatal suspected diagnosis of duodenal atresia according to the ultrasound findings of a "double bubble" and polyhydramnios (at 35 weeks of gestation). No prenatal testing (maternal serum screening or fetal karyotype) was performed. He was born by cesarean section after 35 weeks of gestation. Apgar scores were 8 and 9 at 1 and 5 min respectively. Weight was 1710 g (<3th centile, 50th centile for 31 weeks gestational age), length 42.5 cm (<3th centile, 50th centile for 33 weeks gestational age), head circumference 30.5 cm (<10th centile, 50th centile for 32 weeks gestational age).

At birth his dysmorphic features were trigonocephaly with ridging of the metopic suture, normal inner canthal distance (2.4 cm, 50th centile), epicanthal folds, severe bitemporal narrowing with elonged face, low set and posteriorly rotated ears with abnormal helices, anteverted nostrils, smooth and long philtrum, macrostomia, thin upper lip and everted lower lip, high narrow palate, bilateral camptodactyly of the III and IV fingers and cryptorchidism (Fig. 1B). Trigonocephaly with ridging of the metopic suture may be responsible for the normal inner canthal. Neurological examination showed axial hypotonia (trunk and limb girdle) of central origin; cranial nerve functions were normal. An abdominal X-ray confirmed the presence of a "double bubble" due to a dilated fluid-filled stomach and proximal duodenum. Therefore, a total parenteral nutrition regimen was started. Cardiologic evaluation with electrocardiogram and echocardiography and abdominal ultrasound findings were unremarkable. A transfontanellar ultrasound investigation showed bilateral grade I intraventricular hemorrhage, bilateral periventricular hyperechogenicity with mild symmetrical ventricular dilatation and the persistence of a cyst of the septum pellucidum. An exploratory laparotomy revealed an annular pancreas with an atretic region in the first portion of the duodenum. A side-to-side duodenostomy was then performed. A three-dimensional bony surface computerized tomography (CT) scan of the head confirmed the clinical evidence of metopic synostosis; brain CT scan showed supra and subtentorial bilateral mild ventricular enlargement, marked and diffuse white matter hypodensity and persistence of a cyst of the septum pellucidum and cavum vergae. BAER recordings were obtained only in response to 110-dB nHL intensity click, revealing a severe bilateral conductive hearing impairment and FVEP were abnormal showing a low voltage and prolonged P200 latency (390 msec).

At seven months of corrected age the child showed a severe neurodevelopmental delay and brain MRI showed white matter malacia with cerebral atrophy and hypoplastic corpus callosum.

Table 1
Patient 1; probes flanking the breakpoints.

Probes	Distal nucleotide position (hg18)	Proximal nucleotide position (hg18)	Cytogenetic band	Results
A_14_P113099	59.866.968	59.867.027	2p16.1	+/+
A_14_P127877	60.457.592	60.457.651	2p16.1	−/+
A_14_P125332	61.100.294	61.100.353	2p16.1	−/+
A_14_P133484	61.127.024	61.127.083	2p16.1	+/+
A_14_P126643	66.761.677	66.761.736	6q12	+/+
A_14_P128025	67.314.301	67.314.360	6q12	−/+
A_14_P129092	68.244.706	68.244.765	6q12	−/+
A_14_P131450	68.383.776	68.383.835	6q12	+/+