European Journal of Medical Genetics 55 (2012) 362–366

Contents lists available at SciVerse ScienceDirect

European Journal of Medical Genetics

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

Molecular cytogenetic characterization of an interstitial deletion of chromosome 21 (21q22.13q22.3) in a patient with dysmorphic features, intellectual disability and severe generalized epilepsy

Angelo Valetto [a,*], Alessandro Orsini [b], Veronica Bertini [a], Benedetta Toschi [a], Alice Bonuccelli [b], Francesca Simi [b], Irene Sammartino [b], Grazia Taddeucci [b], Paolo Simi [a,1], Giuseppe Saggese [b,1]

[a] Cytogenetics and Molecular Genetic Unit, A.O.U. Pisana, Ospedale S. Chiara, via Roma 57, Pisa 56100, Italy
[b] Neurological Section, Pediatric Department, A.O.U. Pisana, Ospedale S. Chiara, Pisa, Italy

ARTICLE INFO

Article history:
Received 4 January 2012
Accepted 29 March 2012
Available online 24 April 2012

Keywords:
Epilepsy
FISH
Array CGH
Chromosomal imbalance
Deletion 21q22
DYRK1
KCNJ6

ABSTRACT

We report on a *de novo* interstitial deletion of chromosome 21q in a patient presenting with characteristic facial features, intellectual disability, and epilepsy. The deletion extent was about 4.9 Mb from position 37713441 bp (21q22.13) to position 42665162 bp (21q22.3) (NCBI36/hg18 map).

Patients with partial monosomy 21 are quite rare; this anomaly has been associated with a wide spectrum of clinical signs, ranging from very mild to quite severe phenotypes. This variability results from variability in the deleted regions, thus accurate molecular definition of the chromosomal breakpoints is necessary to make better genotype-phenotype correlations.

We compared our patient's phenotype with the few other patients reported in the literature and found to have similar deletion when analyzed by array CGH. The minimal overlapping region contains only two genes, *DYRK1A* and *KCNJ6*, which may play a major role in these patients' phenotype.

1. Introduction

1.3 We report on a child with distinctive facial features, intellectual disability and severe generalized epilepsy; CGH array revealed an interstitial deletion of chromosome 21 from position to 37713441 bp to position 42665162 bp (NCBI36/hg18 map). The deletion spans about 4.9 Mb, and contains more than 35 genes.

2. Clinical characteristics of the patient

The patient is an 11-year-old boy, the only child of unrelated parents (Fig. 1). At delivery, mother and father were 26 and 31 years old, respectively. The patient was born at 28 weeks gestational, with a birth weight of 1080 g (53rd centile, 0.08 SDS, appropriate for gestational age-AGA). Family history was unremarkable for congenital anomalies, intellectual disability and epilepsy.

His developmental milestones were delayed: he was able to sit autonomously at 10 months, started walking with support at 36 months with balance difficulties, and demonstrated no speech at the age of 11. Feeding difficulties required enteral feeding during infancy. At age 12 months he had several episodes of tonic-clonic generalized febrile seizures, and at age 16 months he started to have generalized tonic-clonic afebrile seizures.

At age 5 years he demonstrated microcephaly (<−2 SD), triangular face, microretrognathia, thin upper lip, hypoplasic alae nasi, long palpebral fissures, large ears and small hands (about 9.8 cm, <3rd centile) and feet (13.9 cm, <3rd centile). His weight was −2.5 SD, and height −2.4 SD. He showed severe intellectual disability (ID), with absent expressive language and extremely limited attention span and object manipulation. He could only walk with support and had no sphincter control.

Routine blood, plasma and urine investigations were in the normal range; platelet count as well as other blood counts were in the normal range; ultrasound of abdomen and heart revealed no abnormalities. Eye evaluation was normal and he had moderate bilateral neurosensorial hypoacusia, and despite use of a hearing aid he could not speak.

Sleeping and awake EEG records showed significant paroxysmal abnormalities (spikes, polispikes and sharp–wave complexes) in the frontocentrotemporal regions, which were bilateral and synchronous, with poorly organized background activity. Brain MRI

* Corresponding author. Tel.: +39 050 992 777; fax: +39 050 992 103.
E-mail address: a.valetto@ao-pisa.toscana.it (A. Valetto).
[1] These two authors equally contributed to this work.

1769-7212/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmg.2012.03.011

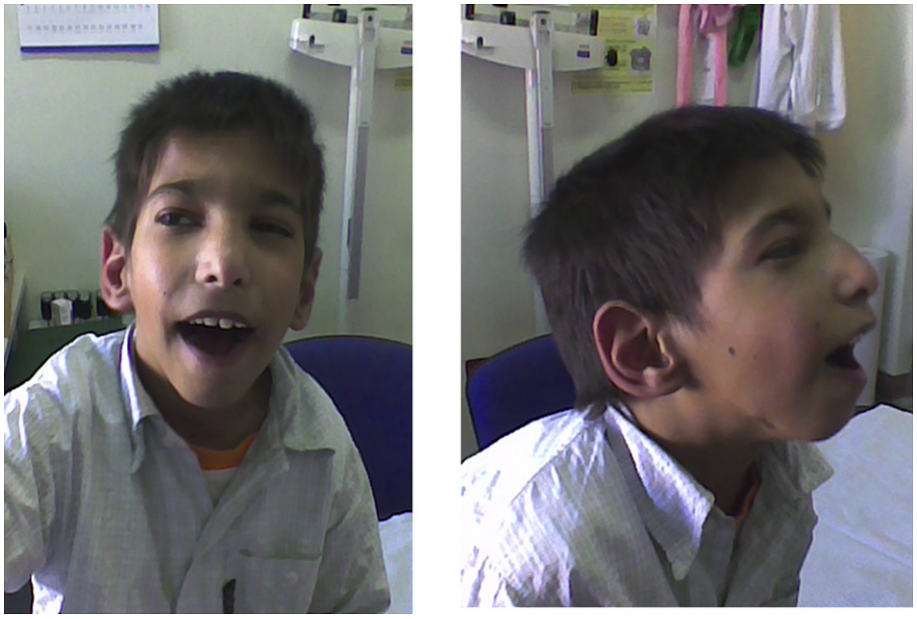

Fig. 1. Patient (frontal and lateral view). Note the triangular face, microretrognathia, thin upper lip, full upper eyelids and cheeks, large, low-set ears, anteverted nares, down-turned corners of the mouth and dental anomalies.

showed diffuse periventricular hyperintensity, more evident at level of the trigones and the posterior portions of celia media, most likely a neonatal sequela. The posterior corpus callosum was hypoplastic, and the sella turcica cavity was small with hypoplasia of the pituitary stalk (Fig. 2).

Thyroid function tests and neurometabolic screenings were normal.

The child manifested numerous episodes of febrile and afebrile seizures, drop attacks and tonic-clonic convulsions. Initially, these seizures were well controlled with valproic acid, clonazepam and phenobarbital, with a few episodes per year up to the age of 8 years.

He returned for evaluation at age 9 years because of weekly seizures that could not be controlled by pharmacological treatment. EEG showed abnormalities prevalent in the centrotemporoposterior regions; valproic acid was changed to carbamazepine with initial improvement of seizures control.

At age 10 years and 9 months, speech was still completely absent and his ID was severe. His height was 117 cm (<3rd centile, −3.6 SDS), with height age 6.4 years, and bone age 7 years, and mid parental height 168 cm (−1 SDS). He was prepubertal and 19.5 kg (<3rd centile). Growth hormone was normal, with low plasma levels of Insuline-like Growth Factor 1 (IGF-1) (2-3 SD below mean). His epilepsy was resistant to his current therapy with carbamazepine, phenobarbital and clonazepam, and his EEG showed a worsening of the bilateral paroxysmal abnormalities.

2.1. Methods and results

Cytogenetics: G and Q banded karyotype of cultured peripheral blood appeared normal.

Array CGH (Array-Comparative Genomic Hybridization) using a 44K oligo platform (Agilent Technologies, Santa Clara, California) detected a *de novo* interstitial deletion of chromosome 21, from position 37713441 bp (q22.13) to position 42665162 bp (q22.3) (Fig. 3); the array CGH fluorescent ratio was about −0.8, suggestive of a mosaic deletion (NCBI36/hg18 map). This result was confirmed by FISH, using the probe LSI 21 (D21S59-D21S341-D21S259) (Vysis,

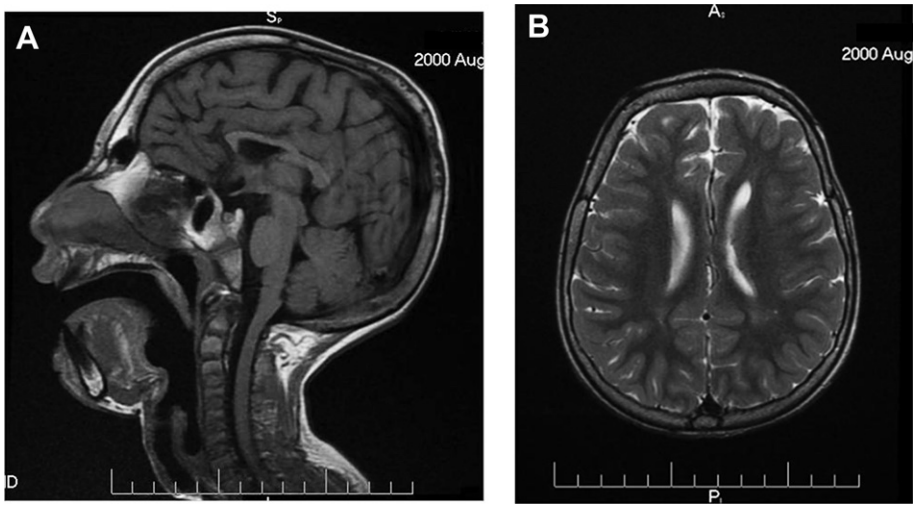

Fig. 2. MRI images. A. midsagittal section. B. transversal section.