European Journal of Medical Genetics 55 (2012) 59–62

Contents lists available at SciVerse ScienceDirect

European Journal of Medical Genetics

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

Original article

2q23.1 microdeletion of the *MBD5* gene in a female with seizures, developmental delay and distinct dysmorphic features

Grace J. Noh, John M. Graham Jr. *

Medical Genetics Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd, PACT, Suite 400, Los Angeles, CA 90048, USA

ARTICLE INFO

Article history:
Received 22 July 2011
Accepted 4 October 2011
Available online 24 October 2011

Keywords:
MBD5
Epilepsy
Mental retardation
Cognitive disability
2q23.1 deletion
Dysmorphic features

ABSTRACT

We report a 2-year-old female who initially presented with seizures, developmental delay and dysmorphic features and was found to have a 0.3 Mb deletion at chromosome 2q23.1 encompassing the critical seizure gene, *MBD5*. Her distinct physical features include bifrontal narrowing with brachycephaly, low anterior hairline, hypotonic facial features with short upturned nose, flat nasal bridge, hypertelorism, tented upper lip with everted lower lip, downturned corners of her mouth, and relatively coarse facial features including thickened tongue. She also had a short neck, brachytelephalangy, clinodactyly, and hypertrichosis. At 3½ years she developed progressive ataxia and lost vocabulary at the age of 4. Regression has been reported in one other case of *MBD5* deletion. *MBD5* is a member of the methyl binding gene family and appears to be responsible for regulating DNA methylation in the central nervous system. Our patient was entirely deleted for the *MBD5* gene with partial loss of the *EPC2* gene, which suggests that haploinsufficiency of *MBD5* is responsible for the distinct phenotype observed. This supports the hypothesis that *MBD5* is indeed the critical gene implicated for the findings seen in patients with deletions of chromosome 2q23.1. Further studies are necessary to delineate the role that the *MBD5* gene plays in the development of the brain and these specific physical characteristics.

1. Introduction

Chromosomal microarray is now considered a first tier clinical diagnostic test for individuals with developmental delay or congenital anomalies [1]. Due to its increased sensitivity, the microarray offers a much higher diagnostic yield (15–20%) than the previously utilized G-banded karyotyping technique (3%). Additionally, chromosomal microarray has also been helpful in identifying the genetic defect in 10–30% of individuals with seizures [2,3]. The highly informative nature of this test has helped to identify many new deletion and duplication syndromes, with subsequent delineation of specific findings associated with each identifiable syndrome as more cases have been reported.

Previous publications of the chromosome 2q23.1 deletion syndrome have delineated a distinct clinical entity [4–8]. The phenotype described in previously reported cases has included seizures, developmental delay, microcephaly, and ataxia in addition to specific facial dysmorphic features.

2. Materials and methods

Oligonucleotide array comparative genomic hybridization (CGH) was performed using the U-array Cyto6000 array platform (Human Genome build: hg18) performed through the University of Utah Cytogenetics Program at ARUP Laboratories, with genomic DNA extracted from peripheral blood.

3. Clinical report

Our patient presented at 2½ years of age with a history of developmental delay, generalized hypotonia and recent onset of seizures. She was born to a 34-year-old mother and 36-year-old father with a negative family history. Her pregnancy, labor and delivery were uncomplicated. Her birth weight, length and head circumference were all at the 50th percentile. She was noted to have global developmental delay and generalized hypotonia at age 12 months, prompting referral for physical therapy, occupational therapy, and speech therapy, where she made slow and steady progress, walking at 28 months and using two-word sentences at 30 months. At 2½ years, she developed generalized tonic–clonic seizures. An MRI of the brain revealed bilateral high signal in the medial temporal lobes on the FLAIR study, slightly more prominent on the left.

* Corresponding author.
E-mail address: john.graham@cshs.org (J.M. Graham).

1769-7212/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmg.2011.10.001

On our initial evaluation at age 2½ years, her height, weight and head circumference were all at the 30th percentile for age. We noted dysmorphic features including brachycephaly, narrow bifrontal diameter with mild ridging of the metopic suture, low frontal hairline, hypotonic facial features with short upturned nose and midface hypoplasia (Fig. 1). She had a square face with relatively coarse features including a tented upper lip, everted lower lip, downturned corners of her mouth, and thick tongue. Other features included a short neck with redundant posterior neck skin, bilateral fifth digit clinodactyly, brachytelephalangy (Fig. 1), generalized hypotonia, and hypertrichosis (Fig. 1).

She was followed by neurology for intractable seizures and tried on several different antiepileptic agents. Her EEG demonstrated multiple bilateral foci of seizure activity. By age 3, her MRI brain had normalized, and the previously seen bilateral bright FLAIR signals in the medial temporal lobes were no longer visualized. She has been seizure free since initiation of a modified Atkins gluten-free ketogenic diet without the use of antiepileptic agents.

Around 3½ years of age, following a viral upper respiratory infection, she developed progressive ataxia. Her work-up revealed a disorganized background without epileptiform activity on EEG, mild diffuse atrophy on her brain and spine MRI, with normal EMGs.

Our follow-up evaluation at age 4 years noted significant regression. Using the Denver II Developmental Assessment tool, we determined that at age 4 years, her gross motor abilities were at the 9-month level. Although she was able to walk independently at 28 months, at age 4 years, she was able to stand only with support. She had always had difficulty with expressive language, but at age 4 years, she had lost some of her vocabulary. She was able to name people and pictures, and point to body parts, placing her at the 24-month level. In terms of her fine motor abilities, she was able to scribble and place 2 cubes to form a tower, but was unable to put clothes on by herself, a 20-month skill. She had deceleration of growth with height 90.5 cm (3–4 standard deviations below the mean expected for age), weight 16.3 kg (25th centile for age), head circumference 48.5 cm (10th centile for age). Her dysmorphic features remained unchanged. She appeared well and was interactive and able to follow simple commands (e.g. point to your nose). However, she appeared uncoordinated with difficulty in balancing. Upon standing, she had a wide stance, locked her knees and was unable to even initiate the normal motions associated with walking. She was able to use a few words with imprecise articulation, possibly due to her thick tongue. Examination of her cranial nerves, muscle bulk and tone, and deep tendon reflexes was all within normal limits, except for several beats of ankle clonus bilaterally.

4. Results

A chromosomal microarray showed a de novo 0.3 Mb deletion involving 6 oligonucleotides within 2q23.1 (Fig. 2) with base pair coordinates 148,867,234–149,172,531. Flanking normal clones 148,238,231 and 149,258,695 were not detected. These findings were confirmed with FISH probe (RP11-375H16) within the abnormal region. This deletion results in loss of one copy of the *MBD5* gene (OMIM 611472) and partial loss of the *EPC2* gene (OMIM 611000).

5. Discussion

The 2q23.1 microdeletion was reported in 2009 by Jaillard et al. [5] in a description of two patients with a similar “pseudo-Angelman” phenotype, including severe psychomotor retardation, speech impairment, epilepsy, microcephaly, ataxia and behavioral

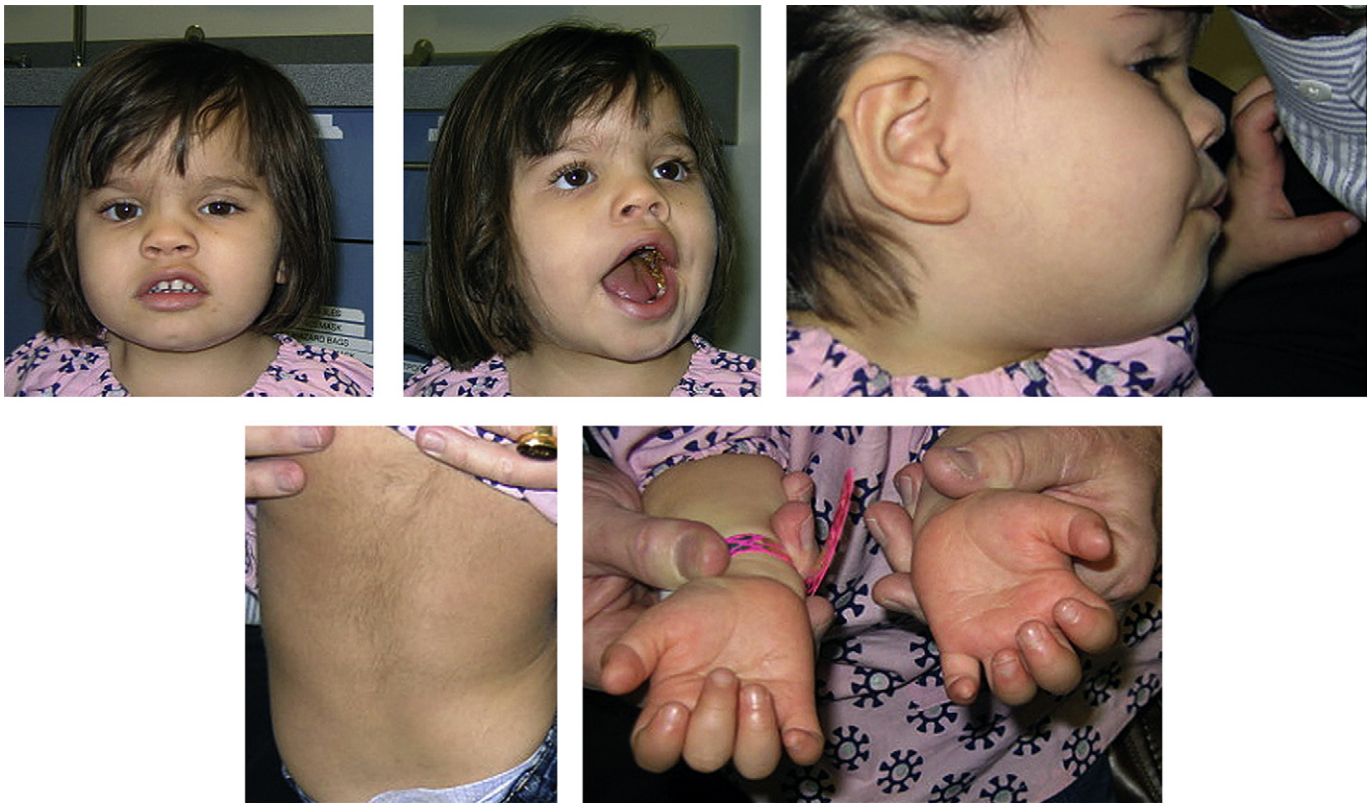

Fig. 1. Frontal and profile view demonstrating square shaped face, coarse facial features including thick tongue, hypertelorism, flat midface, upturned nose, Darwinian tubercle and short neck at 2.5 years of age. Our patient also demonstrated brachytelephalangy and hypertrichosis.