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Clinical and Molecular Characterization of a Patient with a 2p22.3 to 2q24.1 Deletion

KEYWORDS: Array-comparative genomic hybridization (array-CGH), microdeletion, 2p12, 2q22.3, 2q24.1

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ABSTRACT **Background:** *Most of the reported cases with 2q interstitial deletion have been detected by banding cytogenetic techniques. Applying array-based comparative genomic hybridization (array-CGH), the detection rate of submicroscopic chromosomal abnormalities improved considerably.*

Case report: *Here we report on an Albanian boy, five years old, with mental retardation, hypotonia, dysmorphic features and hand/foot abnormalities. A complex cryptic rearrangement of chromosome 2 including a small deletion in 2p12 (547kb, chr2: 75, 145, 737-75, 692, 546) bp) that overlaps with copy-number variant region and a deletion 2q22.3 to 2q24.1 (9.4 Mb, chr2: 145, 809, 240-155, 187, 403) encompassing relevant genes was identified by array-CGH 180 K (Agilent hg19).*

Conclusion: *Our case provide further evidence for the existence of a microdeletion 2q23q24 syndrome and adds new information potentially critical region, involved genes and clinical features*

INTRODUCTION

Banding cytogenetic analysis revealed to date more than 100 individuals with constitutional deletions within the long arm of chromosome 2 and in particular, over 30 with an interstitial deletion (1, 2, 3). There are earlier reports that suggest the presence of a 2q23q24 microdeletion syndrome as a neurocognitive disorder characterized by moderate to severe intellectual disability, hypotonia and feeding difficulties, seizures, stereotypic hand movements, sleep disturbances, short attention span and autistic-like behaviors and abnormal physical features (4, 5). Previously is reported that haploinsufficiency of *MBD5* is the primary causal factor in 2q23.1 microdeletion syndrome and that mutations in *MBD5* are associated with autism (4). Here we describe an Albanian patient carrying two de novo interstitial deletions in 2p12 and 2q22.3-2q24.1. Size and breakpoint of the deletions were determined by array-CGH.

CASE REPORT

A mentally retarded 5-year old Albanian boy was the first child of a 28 years-old mother and 32 years-old father. The parents were healthy and non-consanguineous without any family history. The patient was born at term after an uneventful pregnancy by normal delivery (birth weight 3,700 g; length 50 cm; head circumference 33 cm; APGAR 8/8). During the neonatal period a diffuse hypotonia, hand/foot abnormalities and bilateral cryptorchidism were diagnosed. A delay in motor development was noted from the first month of life with head control achieved at 7 months and sitting at 14 months of life. The patient had his first genetic evaluation at 2 years and 5 months. At this age his weight was 12 kg, height 82.3 cm and cranial circumference 43 cm. On neurogical examination the child showed a developmental and mental delay. At physical examination he presented microcephaly with mild micrognathia, flat nose and the eyebrows were widely separated. He tended to have an open-mouthed with downturned corners and he had bilateral cryptorchidism. Additional features were complete cutaneous syndactyly between third and fourth finger and partial cutaneous syndactyly between second and third finger of the right hand, complete cutaneous syndactyly between the second, third and fourth fingers and partial cutaneous syndactyly between fourth and fifth finger of the left hand.

Also bilateral partial syndactyly of the second and third toe and a sandal gap between the first and second toe were present. Echocardiography, brain MRI scan and abdominal ultrasounds did not find any additional abnormalities. Hearing and vision were normal, still he had absence speech, but a normal EEG. The patient developed generalized seizures at 4 years and 6 months. At this age his weight was 16.5 kg, height 98 cm and head circumference 44 cm. He had reasonable understanding of simple language, but had limited speech. He presented sleep disturbances and behavioral problems (inappropriate laughter and self-biting of hand-shouting), his coordination enabled only poor walk with a broad base, he dressed himself and spoke in 2–3 word sentences. Under treatment, epilepsy was well controlled. Peripheral blood was cultivated and GTG-banding of chromosomes was done at a resolution of 450 bands according to standard procedures according to the International System for Human Cytogenetic Nomenclature 2013 (ISCN 2013) (6). Cytogenetic analysis revealed a normal male karyotype 46, XY and any structural chromosomal abnormality was detected. For this reason array comparative genomic hybridization (array-CGH) analysis was performed using the Agilent's 180 K microarray platform. Array-CGH identified an interstitial deletion of 547 Kb in the short arm of chromosome 2p12 spanning positions 175, 145, 737 to 75, 692, 546 and an interstitial dele-

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tion 9.4 Mb in the long arm of chromosome from 2q22.3 to 2q24.1, spanning positions 145, 809, 240 to 155, 187, 403 (Figure 1a, 1b and 1c).

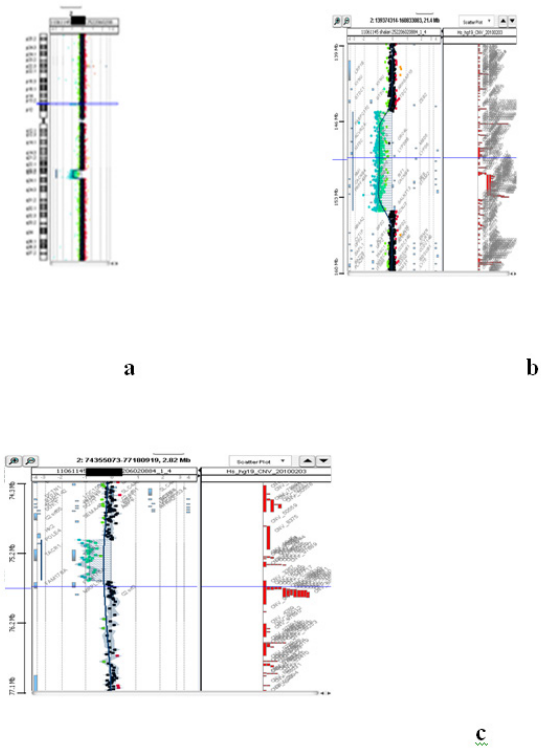

Figure 1. Array-CGH result for chromosome 2, the 9.4 Mb interstitial deletion interval in 2q22.3–q24.1 (hg19, chr2: 145, 809, 240bp – 155,187,403bp) and 547 kb intersticial deletion interval in 2p12 (hg19, chr2: 75, 145, 737bp - 75, 692, 546bp) is clearly visible on the whole chromosome depiction. b) Enlarged view for aberrant region in 2q. c) Enlarged view for aberrant region in 2p.

The molecular cytogenetic karyotype according to ISCN 2013 was designated as: arr 2p12 (75, 145, 737-75, 692, 546) x1, 2q22.3q24.1 (145, 809, 240-155, 187, 403) x1. Array CGH analysis of the parents showed no abnormalities demonstrating a "de novo" origin of the 2p and 2q deletion in the patient.

DISCUSSION

We present a new, clinically abnormal case with a deletion comprising the region 2q22.3q24.1 and additionally 2p12 identified by array-CGH. There are earlier reports of patients with deletions that include overlapping chromosomal subdomains (Decipher database (https://decipher.sanger.ac.uk/), and Maas *et al*. suggest the presence of a 2q23q24 microdeletion syndrome and provide an overview of nine patients (7-8). Common phenotypes observed in those patients and other studies are severe intellectual disability and motor delay, hypotonia, feeding difficulties, seizures, stereotypic hand movements, sleep disturbances, short attention span and autistic-like behaviors. The patients exhibit severe language impairment, often not being able to speak meaningful words. Physical features of patients include craniofacial abnormalities as microcephaly, flat nose, thick arched eyebrows, broad forehead, downturned mouth and thin upper lip, genital anomalies and hand/foot abnormalities (4,5,9,13).

The present case shares some clinical features with previously reported carriers of deletions within the chromosomal region 2q22 to 2q24.

The deleted region 2q22.3–2q24.1 encompasses nine known or predicted genes PABPCP2, ACVR2A, ORC4 L, MBD5, EPC2, KIF5C, LYPD6B, LYPD6, and MMADHC (14).

Haploinsufficiency of *MBD5* gene is associated with microcephaly, intellectual disabilities, severe speech impairment, and seizures. (11,13,15). Previously is reported that haploinsufficiency of *MBD5* is the primary causal factor in 2q23.1 microdeletion syndrome and that mutations in *MBD5* are associated with autism (4, 5).

Besides MBD5 being a likely common pathological defect 2q23q24 microdeletion syndrome (9, 12, 14) *EPC2* gene is also discussed to be involved in mental retardation (13, 16).

To the best of our knowledge, the deletion of 2p12 has been transmitted without consistent phenotypic consequences in more than one independent family. Also this deleted region overlaps with copy-number variant region. So, considering the "two-hit-model" (17) in the deletion of 2p12, an influence of such "copy number variants" cannot be completely neglected and suggest other studies. Our case provides further evidence for the existence of a microdeletion 2q23q24 syndrome and adds new information potentially critical region, involved genes and clinical features.

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