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Chromosomal imbalance report

De novo microdeletions of chromosome 6q14.1-q14.3 and 6q12.1-q14.1 in two patients with intellectual disability - further delineation of the 6q14 microdeletion syndrome and review of the literature

Kerstin Becker [a,*], Nataliya Di Donato [a], Muriel Holder-Espinasse [b], Joris Andrieux [c], Jean-Marie Cuisset [d], Louis Vallée [d], Ghislaine Plessis [e], Nolwenn Jean [e], Bruno Delobel [f], Ann-Charlotte Thuresson [g], Göran Annerén [g], Kirstine Ravn [h], Zeynep Tümer [h], Sigrid Tinschert [a], Evelin Schrock [a], Aia Elise Jønch [i], Karl Hackmann [a]

[a] *Institut für Klinische Genetik, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Fetscherstraße 74, 01307 Dresden, Germany*
[b] *Service de Génétique Clinique, Hôpital Jeanne de Flandre, CHRU Lille, France*
[c] *Institut de Génétique médicale, Hôpital Jeanne de Flandre, CHRU Lille, France*
[d] *Service de Neuro-pédiatrie, Hôpital Roger Salengro, CHRU Lille, France*
[e] *Service de Génétique, CHRU Caen, France*
[f] *Centre de Génétique Chromosomique, Saint-Vincent de Paul, GHIC Lille, France*
[g] *Dept. of Immunology, Genetics & Pathology, SciLifeLab, Uppsala University, Uppsala, Sweden*
[h] *Applied Human Molecular Genetics, Kennedy Center, Glostrup, Denmark*
[i] *Kennedy Center, Genetic Counseling Clinic, Glostrup, Denmark*

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ABSTRACT

Interstitial 6q deletions can cause a variable phenotype depending on the size and location of the deletion. 6q14 deletions have been associated with intellectual disability and a distinct pattern of minor anomalies, including upslanted palpebral fissures with epicanthal folds, a short nose with broad nasal tip, anteverted nares, long philtrum, and thin upper lip. In this study we describe two patients with overlapping 6q14 deletions presenting with developmental delay and characteristic dysmorphism. Molecular karyotyping using array CGH analysis revealed a *de novo* 8.9 Mb deletion at 6q14.1-q14.3 and a *de novo* 11.3 Mb deletion at 6q12.1-6q14.1, respectively. We provide a review of the clinical features of twelve other patients with 6q14 deletions detected by array CGH analysis. By assessing all reported data we could not identify a single common region of deletion. Possible candidate genes in 6q14 for intellectual disability might be *FILIP1*, *MYO6*, *HTR1B*, and *SNX14*.

1. Methods of detection

1.1. Cytogenetics

1.1.1. Patient 1

Karyotyping by GTG banding analysis at 400 bands resolution (ISCN 2009) did not reveal any chromosomal anomalies. Metaphase chromosome FISH-analyses (Fluorescence in situ Hybridization) for microdeletion syndromes in regions 7q11.23, 22q11, and 10p14 were normal [ish 7q11.23(ELN/LIMK1/D7S613x2), 22q11.2(HIRA/D22S553/D22S609x2, HCFx2), 10p14(D10S585x2)].

1.1.2. Patient 2

Routine cytogenetic investigation on peripheral blood was performed shortly after birth. Chromosome analysis using standard Q-banding techniques at band level 450–500 on metaphases were performed on cultured leukocytes and revealed a normal female karyotype. FISH-analyses for microdeletions in region 22q11.2 and 8q24 were normal [ish 22q11.2(D22S(553,609,942)x2), 8q24(767E8x2)]. Subtelomeric rearrangements were investigated by multisubtelomere FISH-analyses (Cytocell) and also gave normal results.

1.2. Array CGH analysis

1.2.1. Patient 1

Molecular Karyotyping was performed by using the Human Genome CGH Microarray Kit 244A (Agilent, Santa Clara CA, USA). Scanning of the hybridized array was carried out on an Agilent

* Corresponding author. Tel.: +49 351 4585138; fax: +49 351 4584316.
E-mail address: kerstin.becker1@tu-dresden.de (K. Becker).

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microarray scanner. Raw data were processed with the Feature Extraction 9.5.3.1 software (Agilent). Deleted or amplified regions were calculated using the ADM-2 algorithm of Agilent's Genomic Workbench Standard Edition 5.0. Customized array CGH designs were generated on Agilent's earray platform (https://earray.chem.agilent.com/earray/).

1.2.2. Patient 2

The array analysis using Affymetrix® Cytogenetic Whole-Genome 2.7M array was performed according to the manufactures instructions. Raw data were processed using ChAS software (Affymetrix).

1.3. Chromosomal anomalies

1.3.1. Patient 1

DNA microarray analysis revealed an approximately 8.9 Mb deletion at 6q14.1-q14.3 (positions of first and last deleted oligos: chr6:76,343,159–85,247,699, UCSC Genome Browser, GRCh37/hg19, http://genome.ucsc.edu). The maximum size of the deletion is 8.94 Mb (positions of first and last present oligos: chr6:76,333,569–85,270,456, GRCh37/hg19). Furthermore, an approximately 120–138 kb deletion was detected at 1p34.1 (positions of first and last deleted oligos: chr1:45,815,979–45,935,720; positions of first and last present oligos: chr1:45,807,677–45,945,302, GRCh37/hg19) with a maximum size of 138 kb.

1.3.2. Patient 2

The DNA microarray analysis revealed an approximately 11.3 Mb deletion at 6q12.1-6q14.1 (positions of first and last deleted oligos: chr6:68,491,706–79,746,176; positions of first and last present oligos: chr6:68,487,198–79,747,008, GRCh37/hg19).

1.4. Method of confirmation

1.4.1. Patient 1

Metaphase chromosome FISH analysis was performed to verify the deletion at 6q14 and to rule out an inversion of that region. BACs RP11-676E19 and RP11-1057N23 were hybridized only on one chromosome 6 in all cells analyzed, whereas BACs RP11-506N21 and RP1-23D17, flanking the deletion, showed a normal hybridization pattern on both chromosomes 6 in each cell assayed. All aforementioned BACs showed a normal hybridization pattern for both parents. Thus, the 6q14 deletion identified in our patient was confirmed to be *de novo*.

The additional deletion in 1p34.1 was confirmed by customized oligo array CGH. This region only contains the *TESK2*-gene coding for the testis-specific protein kinase 2, which is predominantly expressed in testis and prostate and thus unlikely to contribute to the phenotype described here. Moreover, Custom Oligo array CGH analysis of the parents revealed the same deletion in the patient's father, indicating that the deletion at 1p34.1 most likely is a benign familial copy number variation.

1.4.2. Patient 2

The microarray finding was confirmed by real time quantitative PCR (qPCR) analysis, which also showed that the parents did not have the deletion, hereby confirming it as a *de novo* deletion.

1.5. Causative of phenotype

The interstitial 6q deletions identified in both patients were confirmed to be *de novo*. Moreover, similar deletions in 6q14 have previously been described in other patients with developmental delay and overlapping minor anomalies. Taken together, these data highly suggest that the 6q14 deletion is causative for the observed phenotype.

2. Clinical description

2.1. Patient 1

The male patient is the first child of unrelated parents of German origin. The patient's father required speech therapy as a child and was later diagnosed with ADHD. Father and mother attended normal schools. The mother's brother initially presented with speech delay and attended a special school, but was later placed in a normal school. The mother was 18 and the father 20 years old at the time of the boy's birth.

During pregnancy toxoplasmosis was diagnosed in the 18th gestational week (GW) and treated with antibiotics (Daraprim and Sulfadoxin). Smoking was reported until the 20th GW. The boy was born at 39 weeks of gestation through vaginal delivery with a weight of 2980 g (3rd to 10th centile), a length of 50 cm (10th to 25th centile) and head circumference of 33 cm (3rd to 10th centile). After birth, neonatal jaundice was noted and treated using phototherapy. Otoacoustic emissions after birth were positive. Initially, echocardiographics revealed a patent foramen ovale, narrow aortic arch (not a classical coarctation of the aorta), pulmonary hypertension, as well as insufficiency of the mitral and tricuspid valves. At the age of 7 months, only the narrow aortic arch was still detectable while the other cardiac abnormalities had spontaneously regressed. Cranial ultrasound at the age of 4 months did not reveal any abnormalities. Psychomotor milestones were delayed: sitting without support at 11 months, free walking at 24 months, first words at the age of 24 months, approximately 10 words at the age of 3 years and 8 months. The last examination took place at the age of 12 months. At this time his body weight was 7750 g (<3rd centile), his length 75 cm (25th to 50th centile), and his head circumference 46 cm (10th to 25th centile). Dysmorphic features included head asymmetry, low frontal hairline, synophris, arched eyebrows, upslanted palpebral fissures with epicanthic folds, a small nose, anteverted nares, a thin upper lip, single palmar creases, clinodactyly V, sandal gap of toes, and hypoplastic toe nails (see Fig. 1). Cytogenetic analyses, as mentioned above, and *FMR1*-testing yielded normal results.

2.2. Patient 2

The female patient is the second child of unrelated healthy parents of Danish origin. The family history was unremarkable besides late-onset epilepsy in the father at 30 years of age. Pregnancy and delivery were uncomplicated, and she was born at term with a birth weight of 2828 g (10th to 50th centile), birth length of 48 cm (10th to 50th centile), and head circumference of 34 cm (10th to 50th centile). Apgar scores were 8 and 10 at 1 and 5 min, respectively. At birth she had omphalocele and bladder exstrophy. The intestine was normal. Furthermore, bilateral congenital hip dislocation was noted. She had dysmorphic features including a small face with a prominent forehead, hypotelorism, epicanthic folds, intermitting strabismus, synophrys, broad nasal tip, hypoplastic philtrum, thin upper lip, a small tongue, and pointing chin. Moreover, she exhibited partial (skin) syndactyly of the 3rd and 4th fingers on the left hand, small wide hands, syndactyly of the 2nd and 3rd toes on both feet, and pes planus. She had severe hypotonia and hypermobility. Feeding was difficult due to her hypotonia, sucking difficulties and small tongue. She had severe failure to thrive and recurrent cystitis and respiratory infections leading to hospital admissions. Whole body X-ray examination was normal apart from a high thoracic scoliosis. Brain MRI or CT scan have never