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Chromosomal imbalance letter

A *de novo* 15q13.2q13.3 deletion in a boy with an Angelman syndrome like phenotype

Tuva Barøy [a,b], Doriana Misceo [a,b], Øivind Braaten [b], Johan R. Helle [b], Madeleine Fannemel [b], Petter Strømme [c,d,**], Eirik Frengen [a,b,*]

[a] Institute of Medical Genetics, Faculty of Medicine, University of Oslo, Norway
[b] Department of Medical Genetics, Oslo University Hospital, Ullevål, Norway
[c] Department of Pediatrics, Oslo University Hospital, Ullevål, Norway
[d] Faculty of Medicine, University of Oslo, Norway

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ABSTRACT

We report on a 11-year-old boy investigated for a clinical suspicion of Angelman syndrome (AS) (OMIM 105830) who was found to carry a *de novo* interstitial deletion of chromosome 15q13.2q13.3. The deletion overlaps the critical region for the newly recognized recurrent 15q13.3 deletion syndrome. This is the first report of a patient with 15q13.3 deletion syndrome with clinical features similar to that of AS, thus broadening the phenotypic spectrum associated with the 15q13.3 microdeletion syndrome.

1. Methods of detection

Routine chromosome analysis by G-banding at the 550 band level, Southern blot analysis and sequencing analysis of *UBE3A* (exons 7–16), *MECP2* and *SLC9A6* were performed by standard methods. Array Comparative Genome Hybridization (aCGH) was carried out using a 44K oligonucleotide microarray (Agilent Technologies, Santa Clara, CA) according to the manufacturer's recommendations. Data were processed with Feature Extraction and DNA Analytics v3.4, (Agilent Technologies).

2. Chromosomal anomaly

The laboratory investigations did not support the clinical suspicion of AS: the G-banding revealed a normal 46,XY karyotype; Southern blot analysis did not detect uniparenteral disomy of chromosome 15 and sequencing analysis revealed no *UBE3A* mutations. Mutations in *MECP2* or *SLC9A6* have been detected in males with clinical findings suggestive of Angelman syndrome [4,15], but sequencing of these genes did not reveal any mutations in our patient.

aCGH revealed an interstitial microdeletion in chromosome band 15q13.2q13.3. The minimal deletion is 1.6 Mb and consists of 29 oligos betweenchr15:30938215–32510863bp, hg19 (Fig. 1). The maximal size of the deletion is 2.6 Mb, betweenchr15:30322138–32914081bp, hg19. The oligo names of the first and last abnormal probe is A-14-P126587 and A-14-P105986, respectively. This deletion overlaps with the newly recognized recurrent 15q13.3 deletion syndrome (OMIM 612001), whose critical deleted region maps between the paralogous segments BP4 (chr15:29962708–31462708 bp) and BP5 (chr15:32112708–33612708 bp) (hg19).

3. Method of confirmation

Fluorescence *in situ* hybridization (FISH) was performed using the BAC clone RP11-16E12 (chr15:31489962–31663667 bp, hg19) located within the deleted region, and the BAC clone RP11-697A1 (chr15:100625952–100810994 bp, hg19) as a chromosome 15 control probe. The FISH results confirmed the deletion in the proband (Fig. 2).

* Corresponding author. Institute of Medical Genetics, University of Oslo, P.O. Box 1036, Blindern, N-0315 Oslo, Norway. Tel.: +47 22117825; fax: +47 22119899.
** Corresponding author. Department of Pediatrics, Oslo University Hospital, Ullevål, 0407 Oslo, Norway. Tel.: +47 23015234; fax: +47 23015790.
E-mail addresses: tuva.baroy@medisin.uio.no (T. Barøy), doriana.misceo@medisin.uio.no (D. Misceo), oivind.braaten@medisin.uio.no (Ø. Braaten), j.r.helle@medisin.uio.no (J.R. Helle), Madeleine.Fannemel2@ulleval.no (M. Fannemel), petter.stromme@medisin.uio.no (P. Strømme), eirik.frengen@medisin.uio.no (E. Frengen).

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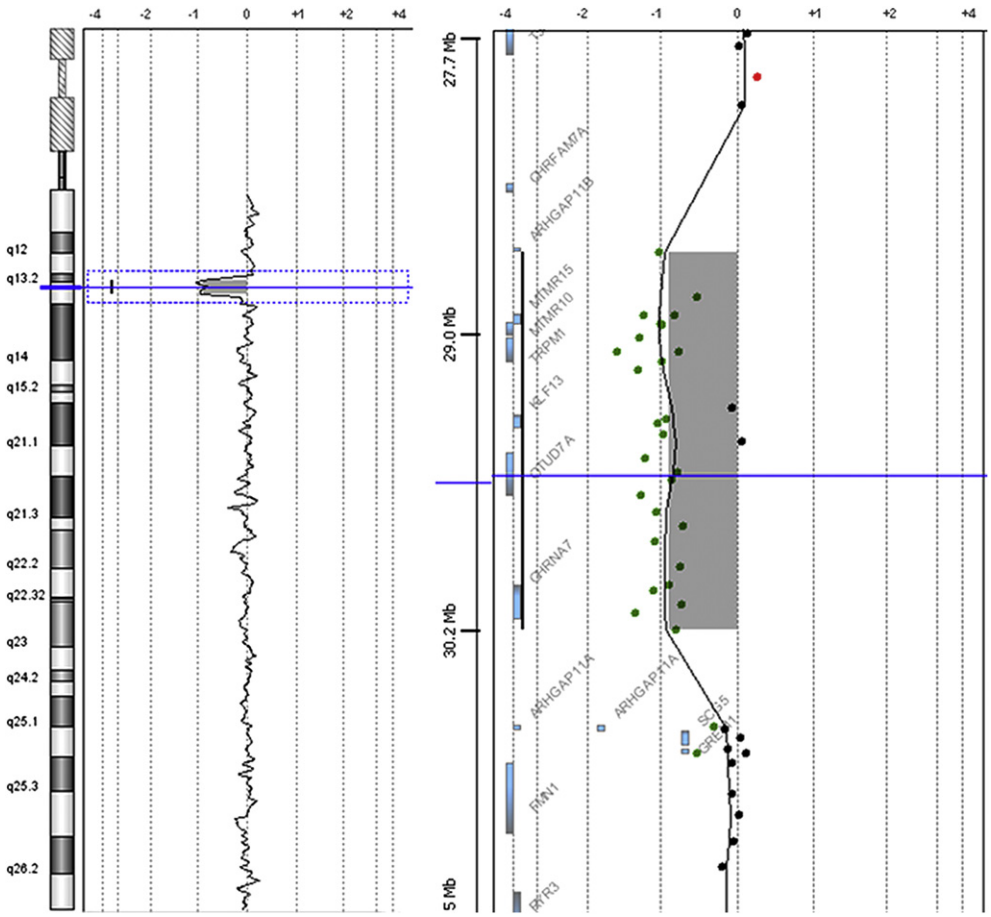

Fig. 1. The graphical output of the aCGH results. On the left, whole chromosome 15; on the right detail of the deleted region (chr15:30938215–32510863, hg19). Dots represent the oligos along the chromosome. In green the oligos in the deleted region (ratio patient in Cy3/Control in Cy5 is lower than −0.4); in black oligos with a normal ratio (−0.4< ratio >0.4). The area highlighted in grey indicates the extension of the deletion.

4. Causative of the phenotype

FISH analysis using the same fluorescent BAC clones as in the patient did not reveal any deletion in the parents, thereby indicating that the deletion found in the patient originated *de novo*.

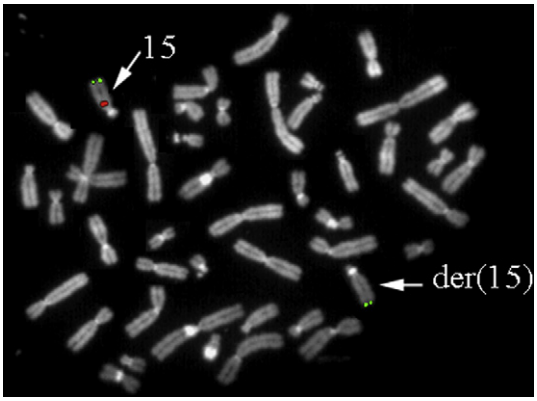

Fig. 2. Verification of the deletion in chromosome 15q13.2q13.3 by FISH. BAC clone RP11-16E12, red (chr15:31489962–31663667 bp, hg19) gives one hybridization signal, thereby confirming the deletion. BAC clone RP11-697A1, green (chr15:100625952–100810994 bp, hg19), gives signals on both chromosomes 15 (used as a chromosome 15 control probe). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The proband has a brother with autistic features, and since autistic spectrum disorder (ASD) is within the phenotypic range caused by chromosome 15q13.3 deletions [8,9], an aCGH analysis (44K oligo array) was performed on this brother. The aCGH did not detect any pathological imbalance, suggesting different etiologies for the two brother's conditions.

5. Clinical description

The patient, a boy, was the second child of a healthy non-consanguineous Norwegian couple. He has three healthy older maternal half siblings and an older brother with autistic features. At the time of birth the mother was 37 years old and the father was 32 years old. Birth weight, length and head circumference were 3810 g (75th centile), 51 cm (50th centile) and 33 cm (<5th centile), respectively. Apgar scores were 9/9/10 after 1, 5 and 10 min. Psychomotor delay was noticed at 7 months; he sat at 12 months and walked at 18 months. As a small child his gait was characterized by poor balance with frequent falls and ankle distortions. Behavioural abnormalities included stereotypic shrugging movements with his upper body and an excessive devotion for playing with water. Initially, AS was suspected due to his neurological features overlapping with this syndrome (Table 1) [16], but relevant laboratory investigations did not confirm this diagnosis. He did not have seizures, except from a possible febrile seizure at 7 months. EEG recorded at age 7 years showed a pathological pattern of high