A 17q21.31 microdeletion encompassing the MAPT gene in a mentally impaired patient

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Abstract. About 15% of patients with a clinical phenotype of Angelman syndrome (AS) have an unknown etiology. We report a patient with features reminiscent of AS, including a pattern of characteristic facial anomalies as well as speech impairment, developmental delay and frequent laughter. In addition, the patient had features not commonly associated with AS such as heart malformations and scoliosis. She was negative in SNURF-SNRPN exon 1 methylation studies and the G-banded karyotype was normal. Array-based comparative genomic hybridization disclosed a deletion of maximally 1 Mb at 17q21.31. The deleted region contains the MAPT gene, implicated in late onset neurodegenerative disorders, and the STH and NP_056258.1 genes. Another gene, such as CRHR1, might also be included based on maximum possible size of the deletion. We suggest that microdeletions within the 17q21.31 segment should be considered as a possible cause of phenotypes resembling AS, particularly when easily controlled seizures and/or cardiac abnormalities are also present.

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Materials and methods

Patient description
Here we report a female patient first seen at 2 years of age who was referred for genetic testing for AS. Informed written consent was obtained from the parents. She was the first child born to non-consanguineous, healthy Caucasian parents at 38 weeks of gestation by Cesarean section. Birth weight was 2,560 g (2.5 < P < 10), length was 44.5 cm.
Camera and processed using ISIS software (MetaSystems, Altlussheim, (Carl Zeiss, Jena, Germany). Metaphases were captured with a CCD analyses were performed under a Zeiss Axiophot epifluorescence microscope hybridized following standard procedures (Rosenberg et al., 1994). Analyses were performed on metaphase spreads from the parents to determine if the deletion had been inherited. Clones shown to be deleted by array-CGH (Fig. 2) were hybridized following standard procedures (Rosenberg et al., 1994). Analyses were performed under a Zeiss Axiophot epifluorescence microscope (Carl Zeiss, Jena, Germany). Metaphases were captured with a CCD camera and processed using ISIS software (MetaSystems, Altlussheim, Germany).

Results and discussion

The patient’s karyotype after GTG-banding at the 550 band level resolution was 46,XX. The analysis of SNURF-SNRPN exon 1 methylation patterns amplified by PCR (Zeschnigk et al., 1997) showed one paternal and one maternal band, and excluded microdeletion of 15q11–q13, UPD and maternal mutation in the imprinting center as causes for the AS phenotype.

Array-CGH was performed on DNA from peripheral blood from the patient as previously described (Rosenberg et al., 2006). Array clones found to be altered in normal controls or with a large standard deviation were excluded, as described in Rosenberg et al. (2005).

The array-CGH disclosed a unique alteration, a deletion of 0.1–1 Mb (Fig. 2A) at 17q21.31, which was confirmed by fluorescence in situ hybridization using the clone located in the deleted segment, namely RP5-843B9 (FISH – Fig. 2B). FISH on metaphases from the parents showed that the deletion of the patient was de novo.

Mickelson et al. (1997) have reported a patient with a phenotype reminiscent of Angelman syndrome and a deletion mapped cytogenetically to the interval 17q23.1–q23.3. They used polymorphic markers to corroborate the supposed location of the cytogenetic deletion but surprisingly failed to show any loss of alleles. Recent information obtained from the Ensembl genome browser confirms that many of the markers used must have been within the cytogenetically determined deletion area. Those markers are physically located within the 17q22–q25 and cover over 22 Mb. Importantly, none of the informative markers would have overlapped the location of the deletion described by us, raising doubts on the accuracy of the estimated cytogenetic location of their deletion; this leaves open the possibility that their deletion could overlap ours. Further, Mickelson et al. (1997) compared their case to four other patients in the literature carrying 17q21–q24 deletions, none of whom exhibited resemblance to the Angelman phenotype. The deletion in our patient is much smaller and more precisely mapped than those described previously and reviewed by Mickelson et al. (1997). Amongst the features most frequently described in their review of patients with 17q21 deletions, our patient exhibited developmental delay, dislocated hips, impaired vision and congenital heart disease, but did not present short stature, microcephaly, symphalangism and proximal thumbs.

Although our patient exhibits some features of AS, her developmental delay is milder and her seizures easier to control than generally observed in AS patients with 15q deletions, and is similar to some AS patients with UPD15. In addition, she does not present ataxic gait, characteristic of AS, and she has features not commonly found in AS such as congenital heart abnormalities and scoliosis.

One other deletion patient detected by the same array-CGH probe (RP5-843B9) was recently reported by Shaw-Smith et al. (2004) in a screening for submicroscopic chromosome alterations in 50 patients with learning disabilities. It is noteworthy that the phenotype of their patient did not resemble AS, and includes short stature, mild contractures and

Fig. 1. Facial appearance of the propositus at the age of 2 (left) and 3 (right) years.

(P < 2.5) and OFC 34 cm (p25). Apgar scores were 9 at 1 min and 10 at 5 min. She presented poor sucking, neonatal hypotonia and mild developmental delay: she could raise her head at 6 months, sat without support at 8 months, walked at 19 months, and started to speak a few words around 2 years of age. At physical examination, she had brachycephaly, occipital groove, upslanting palpebral fissures, hypertelorism, anteverted nares, protruding tongue, micrognathia, wide mouth, short philtrum, wide-spaced teeth, frequent drooling, strabismus, hypopigmented skin, light hair and eye color compared to family members (Fig. 1). Her weight was 11.8 kg (25 < P < 50th centile), height 90 cm (75 < P < 90th centile), and head circumference 47.5 cm (50 < P < 75th centile). She also presented swallowing disorders, heart malformations including atrial septal and ventricular septal defects, and persistent ductus arteriosus, congenital left hip dislocation, scoliosis and impaired vision (hypermetropia). A single clonie seizure episode occurred at age of 13 months but a brain MRI was normal. She exhibited speech impairment with minimal use of words, non-verbal communication, frequent chewing/mouthing behavior, bruxism and attraction to/fascination with water.

Array-CGH

The array-CGH procedures were performed as previously described (Knijnenburg et al., 2005; Rosenberg et al., 2006). Briefly, slides containing triplicates of ~3,500 large insert clones spaced at ~1.0 Mb density over the full genome were produced in the Leiden University Medical Center. The large insert clone set used to produce these arrays was provided by the Wellcome Trust Sanger Institute (UK), and information regarding the full set is available at the Wellcome Trust Sanger Institute mapping database site, Ensembl (http://www.ensembl.org/). DNA amplification, spotting on the slides and hybridization procedures were based on published protocols (Carter et al., 2002; Fiegler et al., 2003). Target imbalances were determined based on log2 ratios of the average of their replicates, and sequences were considered as amplified or deleted when outside the ± 0.33 range.

Fluorescence in situ hybridization (FISH)

FISH experiments were performed on metaphase spreads from the patient to validate the presence of the imbalance identified by array-CGH analyses, and from her parents to determine if the deletion had been inherited. Clones shown to be deleted by array-CGH (Fig. 2) were hybridized following standard procedures (Rosenberg et al., 1994). Analyses were performed under a Zeiss Axiopt epifluorescence microscope (Carl Zeiss, Jena, Germany). Metaphases were captured with a CCD camera and processed using ISIS software (MetaSystems, Altlussheim, Germany).
patchy skin pigmentation. The only feature in common with our patient was mental impairment. A critical comparison between the breakpoints of the deletions would provide a better understanding of the phenotypic effect of genes in the deleted areas.

The segment on chromosome 17 encompassing the deletion in our patient harbors several low-copy repeats (LCR). These LCRs have been recently associated with a 900-kb inversion which is polymorphic with a high frequency (up to 20%) in European populations (Stefansson et al., 2005). This
region contains several genes, including the microtubule associated protein tau gene (MAPT), associated with late onset neurodegenerative disorders such as Alzheimer and the Parkinson-Dementia syndrome (MIM 260540). Other genes within the deleted clone are saitohin (STH), mainly expressed in placenta, muscle, and fetal and adult brains, and NP_056258.1, with unknown function (Swiss-Prot/TrEMBL; http://ca.expasy.org/sprot/). The total possibly deleted area (Fig. 2A) contains other genes with known function, namely CRHR1 (expressed in cerebellum, cerebral cortex, pituitary and olfactory lobe), and NSF, expressed in the central nervous system and diminished in schizophrenic patients (Mirnics et al., 2000). Which genes in this area are involved in the phenotype of our patient remains to be determined.

We suggest that deletion or alteration of one or more genes within this 1-Mb region should be considered as a possible genetic cause for patients resembling the AS phenotype and for whom the well known chromosome 15 mutational mechanisms for AS do not apply, particularly when mild neurodevelopment, easily controlled seizures and/or cardiac abnormalities are present.

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References

Ensembl: http://www.ensembl.org/.