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SHORT REPORT

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An unexpected recurrence of Angelman syndrome suggestive of maternal germ-line mosaicism of del(15)(q11q13) in a Finnish family

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Abstract Angelman syndrome is a neuro-developmental disorder caused by genetic abnormalities affecting the maternal gene expression in the chromosome region 15q11-q13. In a study group of 45 Finnish Angelman patients, a reccurence of a del(15)(q11q13) was detected in one family. The mother's chromosomes 15 were structurally normal, whereas the patients and their unaffected brother shared an identical maternally derived haplotype outside the deletion region. These findings are suggestive of maternal germ-line mosaicism of del(15)(q11q13).

Introduction

Angelman syndrome (AS; MIM 105830) is a rare neuro-developmental disorder with an incidence of 1/15,000 live births. It is characterized by severe mental retardation, absence of speech, ataxic gait and uncoordinated movements, easily provoked smiling and laughter, abnormal electroencephalogram, seizures and dysmorphic facial features (Williams et al. 1995).

AS is caused by a functional lack of maternally imprinted gene(s) at the chromosome region 15q11-q13 because of an interstitial deletion on the maternal chromosome (70%), paternal uniparental disomy (3%), an imprinting defect (7%) or a *UBE3A* gene mutation (5%). In about 15% of Angelman patients, the genetic defect remains unknown (Jiang et al. 1999).

Recurrence of AS is rare but has been observed in some families with either a maternally inherited imprinting centre (Ohta et al. 1999) or a *UBE3A* gene mutation (Fang et al. 1999). We report a family with an unexpected recurrence of a del(15)(q11q13) that is present in two affected sibs and that is probably attributable to germ-line mosaicism in the mother.

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Patients and methods

The two sibs with AS (a 16-year-old boy and a 5-year-old girl) belong to a group of 45 Angelman patients in 43 families studied at the molecular level. The AS diagnosis was made at 8 years and at 3 months of age, respectively. Both parents and the 18-year-old brother were healthy.

Genomic DNA from the patients and their parents was extracted from peripheral blood. Parent-of-origin DNA methylation imprints were determined by using the probes DN34, PW71B and α-SNRPN. For the detection and determination of the size of the deletion and for haplotype analysis, the chromosome-15q11-q13-specific probes ML34 (D15S9), IR4–3R (D15S11), 189–1 (D15S13), hN4Hs (SNRPN), 28β-3H (GABRB3), 3–21 (D15S10), IR10–1 (D15S12) and CMW-1 (D15S24) and the chromosome-15-specific microsatellite markers D15S542, D15S11, D15S128, D15S122, D15S113, GABRB3, D15S97, GABRA5, D15S156, D15S165, D15S118, CYP-19, FES, D15S125 and D15S87 were used as described earlier (Kokkonen et al. 1995).

A high-resolution chromosome study was performed with the GBG method (G bands with bromodeoxyuridine and Giemsa). For one-colour FISH (fluorescence in situ hybridization), digoxigenin-labelled D15S10/PML and SNRPN/PML probes (Oncor) were employed and, for dual-colour FISH, biotin-labelled D15S11 and digoxigenin-labelled D15S10 probes (Oncor) and a D15Z1/SNRPN/PML directly labelled dual-colour probe set (Vysis) were used.

Results and discussion

A molecular abnormality was found in 40 of the 45 patients (89%; Table 1). Twenty-nine patients had a deletion in the chromosome region 15q11-q13. Two of them were sibs who had an identical large interstitial deletion encompassing the region from D15S524 to D15S12 in the maternal chromosome 15. The deletion was also revealed by high-resolution banding and FISH methods (Fig. 1a, b). Both homologues 15 of the parents were cytogenetically normal. No mosaicism of the del(15)(q11q13), by one-colour FISH, or structural changes involving chromosome 15, by dual-colour FISH, could be detected in FISH stud-

Table 1 Molecular findings of 45 Finnish patients with Angelman syndrome (*UPD* uniparental disomy)

Type of change at 15q11-q13	Number of patients	Percentage of total (%)	Methylation pattern	Other observations
Deletion	29	65	Paternal only	Includes a pair of sibs
Paternal UPD	1	2	Paternal only	Error in paternal meiosis II
Imprinting defect[a]	5	11	Paternal only	Includes a pair of sibs
UBE3A mutation[b]	4	9	Biparental	Includes a case with maternal mosaicism
Incompletely characterized[c]	1	2	Paternal only	No deletion detected
Not known	5	11	Biparental	

[a]Two patients (family ASF) reported by Ohta et al. 1999, one patient reported by Buiting et al. 1998

[b]To be reported by K. Rapakko et al.

[c]Parental DNA samples not available

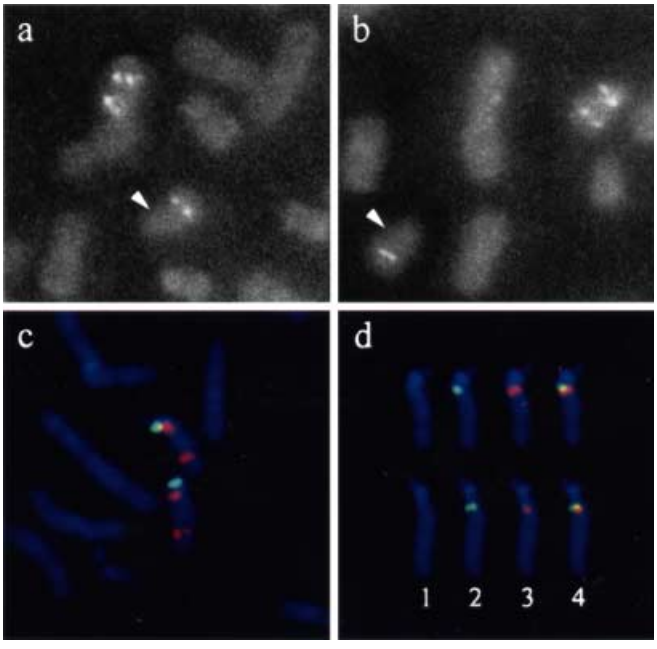

Fig. 1a–d FISH analysis of the family with recurrent del(15)(q11q13). The affected son's (**a**) and his affected sister's (**b**) chromosomes 15 after hybridization with the probes D15S10 (15q12) and PML (control). *Arrowheads* Deletion site. (**c**) The mother's chromosomes 15 hybridized with probes D15Z1 (short arm, *green*), SNRPN (15q12, *red*) and PML (*red*), excluding a deletion, translocation or inversion. (**d**) A composite view of four different staining phases of a single cell showing the mother's chromosome pair 15 in a simultaneous hybridization with D15S11 (15q12, *green*) and D15S10 (15q12, *red*) probes. The order of the loci is cen-D15S11-D15S10-tel. Counterstain (*1*), D15S11 (*2*), D15S10 (*3*) andD15S11 and D15S10 (*4*). No small paracentric inversion was detected

ies of the mother (Fig. 1c, d). The patients and their unaffected brother also showed an identical, maternally derived haplotype distal to the deletion region, suggesting that all three had inherited the same grandpaternal chromosome 15 from the mother. These findings suggest the presence of germ-line mosaicism of del(15)(q11q13) in the mother.

Recurring deletions of 15q11-q13 are extremely rare. So far, in AS, only one recurrent maternal, grandpaternally derived deletion involving the loci D15S113, D15S10 and GABRB3 has been described in two affected sibs (Saitoh et al. 1992). Maternal translocations (Smeets et al. 1992; Burke et al. 1996) or inversions (Webb et al. 1993) involving the chromosome region 15q11-q13 have been reported to lead to deletions responsible for AS in the offspring. In the present family, these mechanisms can be ruled out because the mother's chromosomes 15 are structurally normal.

Germ-line mosaicism has been reported to account for an unexpected recurrence of many genetic diseases and it seems to be more prevalent than expected (see Zlotogora 1998). In AS, germ-line mosaicism for imprinting centre mutations has been reported (Gilbert et al. 1997). The existence of gonadal mosaicism of del(15)(q11q13) has been anticipated (Stalker and Williams 1998) and this family shows that such mosaicism needs to be taken into consideration in genetic counselling.

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