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ARTICLE

Molecular cytogenetic characterization of terminal 14q32 deletions in two children with an abnormal phenotype and corpus callosum hypoplasia

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Among previously reported cases of 14q terminal deletions, only 11 have dealt with pure terminal deletion of 14q (14q3–14qter) and the break points were mapped by fluorescent *in situ* hybridisation (FISH) or genotyping in only four of them. Thanks to a collaborative study on behalf of the 'Association des Cytogeneticiens de langue Française'(ACLF), we report two patients with terminal deletion of the long arm of chromosome 14, del(14)(q32.2) and del(14)(q32.32), diagnosed by subtelomere screening. In the two cases, a thick nuchal skinfold was detected by early ultrasound with normal prenatal karyotype. Their postnatal phenotype included large forehead, narrow palpebral fissures, epicanthic folds, upturned tip of the nose, narrow mouth and thin upper lip, microretrognathia, prominent earlobes, hypotonia, delayed psychomotor development and hypoplastic corpus callosum. By physical mapping using FISH, the size of the deletions was measured for patients 1 and 2: 6.55 ± 1.05 and 4.67 ± 0.10 Mb, respectively. The paternal origin of the deleted chromosome 14 was established by genotyping of microsatellites for patient 1 and the phenotype of terminal del(14)(q32) was compared to maternal uniparental disomy 14.
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Keywords: chromosome band 14q32; 14q telomere; terminal deletion; chromosome 14; corpus callosum

Introduction

Deletions of chromosome 14q are rarely reported. Excluding ring chromosome 14, about 30 previous articles have dealt with distal deletion of chromosome 14q,[1–21] of which only 22 cases affected the 14q3 region. Three of these cases involved autosomal translocations.[2–4] In six other cases, the deletion was associated with either a 20p deletion[5] or a chromosome 14 rearrangement.[6–10] In one case, the deletion appeared to be interstitial.[11,12] In one case, the deletion was associated with mosaicism (46,XX/46,XX,del(14)(q32.3)).[13] Only 11 cases were considered as examples of pure, distal and homogeneous 14q arm deletions[12,14–21] (Table 1).

Most of the reported cases were cytogenetically visible and diagnosed by classical banding. Five cases were diagnosed only by subtelomere fluorescent *in situ* hybridisation (FISH).[3,20,21] If we consider the case of Maurin *et al*,[10] a pure distal 14q deletion since the presence of a terminal NOR region should not have any influence on the

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Table 1 Published cases with 14q3 terminal deletions

Chromosome 14 break point	*Terminal deletion associated with another abnormal segment or clone*	*Pure homogeneous deletion*	*Karyotype*	*FISH*	*STS*	*Deletion size*
14q31	Nielsen *et al*[6]		46,XX/46,XX,inv(14)(q21→q31), del(14)(q31)	—	—	?
	Uehara *et al*[5]		46,XX,del(14)(q32)del(20)(p11)	—	—	?
		Fu Sun Yen *et al*	46,XX, del(14)(q31.1)	—	—	?
14q32	Bregant *et al*[4]		46,XY,der(14)t(10;14)(q24;q32)	—	—	?
		Mertens *et al*[18]	46,XY,del(14)(q32)	—	—	?
14q32.1	Masada *et al*[7]		46,XY,del(14)(q32.11→qter)	—	—	?
	Magnani *et al*[8]		47,XX,+?mar, del(14q32.1–qter)	—	—	?
14q32.2		Wang *et al*[16]	46,XX,del(14q32.2)	—	—	?
14q32.3	Miller *et al*[13]		46,XX/46,XX, del(14)(q32.3)	—	—	?
	Meschede *et al*[2]		45,XY,tan(14;21)(q32.3;p11)	—	—	?
	Chen *et al*[9]		46,XX,der(14)-dup(14)(q32.3q31.3)del(14)(q32.3)	—	—	?
		Telford *et al*[15]	46,XX,del(14)(q32.3)	—	—	?
		Wintle *et al* (patient HSC1363)[12]	46,XX,del(14)(pter→q32.3:)	*DIO3* (101088–101215 kb) deleted	D14S13 (not deleted) D14S1 (deleted) D14S20 (deleted)	>5.3 Mb
14q32.31		Ortigas *et al*[17]	46,XX,del(14)(q32.31)	D14S308 (106175 kb)	—	?
		Van Karnebeek *et al*[19]	46,XX,del(14)(q32.31–qter)	Complete set human subtelomeric probes	D14S985 (100366 kb) not deleted D14S292 (103670 kb) deleted	2.3 Mb <X-<7.2 Mb
14q32.33		Schlade-Bartusiak *et al*[20] (Patient HSC1658)	46,XX deletion diagnosed by FISH	*CKB* (103056–103059 kb) not deleted, *KNS2* (103165–103247 kb) deleted	—	>3.2 Mb
	Leube *et al*[3]		46,XX,der(14)t(9;14)(q34.3;q32.33)	—	—	?
	Maurin *et al*[10]		46,XX,der(14)t(14;D/G)(q32.33;p12)	RP11–1087P8 (not deleted) RP11–417P24 (deleted)	—	1–1.6 Mb
14q?→14qter		Ravnan *et al*[21]	Three patients: deletion diagnosed by FISH	Complete set human subtelomeric probes	—	?

phenotype assuming the absence of position effect, a total of eight cases with pure distal deletion were confirmed by FISH[12,17,19,20,21] and the break points were mapped in only four patients[10,12,19,20] (Table 1).

We report here the clinical findings in two patients with 14q32.2 and 14q32.32 deletions identified by subtelomere screening. Patient 1 had a pure distal 14q32.2 deletion and patient 2 had a deleted derivative 14 chromosome from a paternal cryptic translocation t(14;17)(q32.32;qter). We analysed by FISH the length of the corresponding size of the deletions to contribute to the del(14q) genotype–phenotype correlation. The parental origin of the deletion in patient 1 was established by genotyping of sequence tagged sites (STS) microsatellites. This study has been initiated on behalf of the ACLF ('Association des Cytogeneticiens de langue Française').

Subjects and methods

Patients

Patient 1 This patient was the first child of non-consanguineous Caucasian parents. His father and mother were aged 32 and 28 years, respectively, at the time of his birth. Prenatal ultrasound scans disclosed a thick nuchal skinfold at 11 WG, which prompted chorionic villi sampling (the result showed normal karyotype). Ultrasonography scans during second and third trimesters showed a short corpus callosum, and generalised oedema of the skin. A control karyotype on amniotic fluid cells was considered normal. The child was born at 40 weeks of gestation with a birth weight of 3450 g (50th centile), a length of 49.5 cm (−1 SD), and OFC of 35 cm (M). Brief resuscitation was necessary because of primary apnoea. In the neonatal period, difficulty in swallowing necessitated transient G-tube feeding. At first evaluation at the genetic clinics at age 2 months, the following dysmorphic features were recorded: narrow face, bulging forehead, narrow and upslanted palpebral fissures, marked epicanthal folds, bushy eyebrows, cylindrical nose with wide, upturned tip and shallow root, long philtrum, narrow mouth, normal palate, microretrognathia, prominent, thick earlobes, short neck (Figure 1a and b). The fontanels were widely opened.

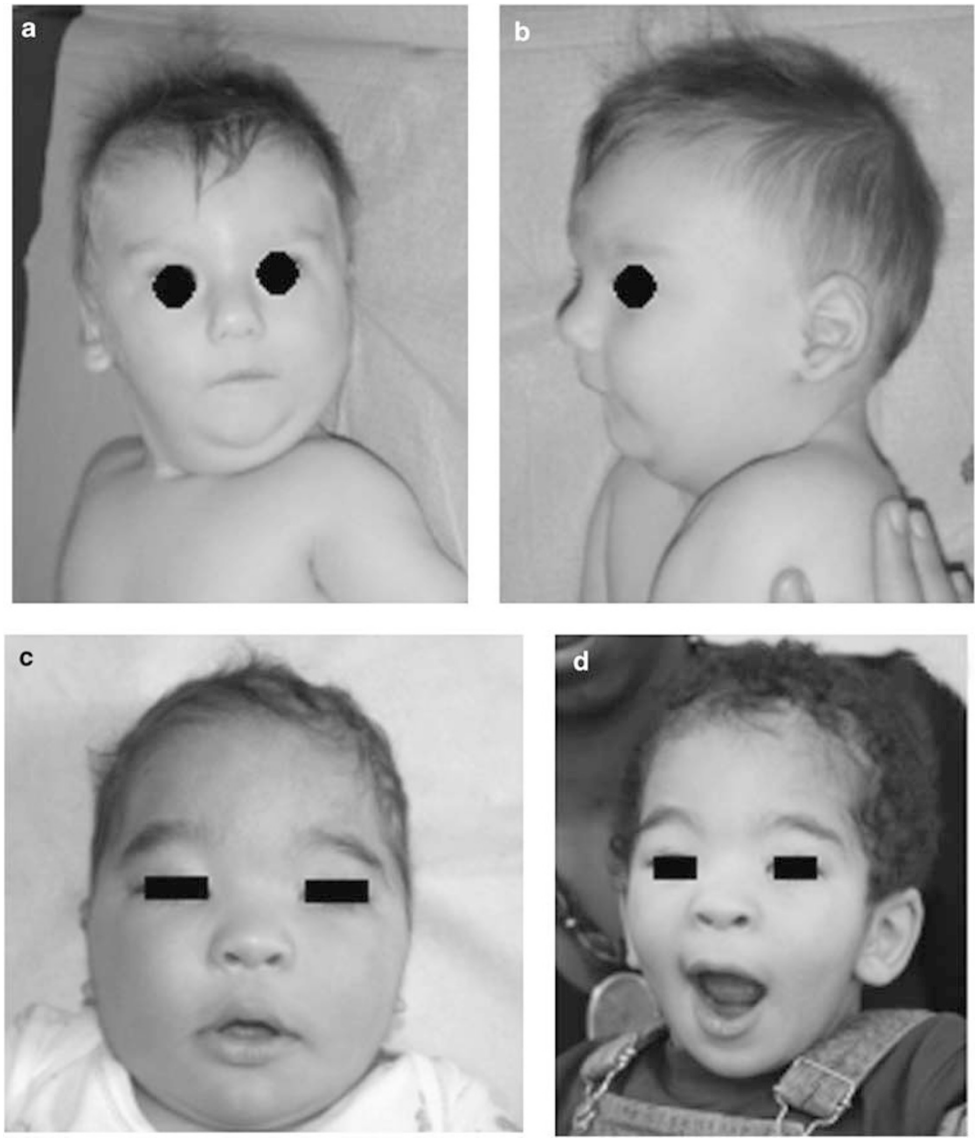

Figure 1 Pictures of patients 1 and 2 showing the dymorphic facial features. Patient 1 at 6 months of age: narrow face, bulging forehead, narrow, upslanted palpebral fissures, marked epicanthal folds, cylindrical nose with wide, upturned tip and shallow root, long philtrum, small mouth, microretrognathia (**a**) and prominent, thick earlobes (**b**). Patient 2 at 1 year (**c**) and 3 years (**d**) of age with hypertelorism, epicanthal folds, long philtrum, tented upper lip, long palpebral fissures, bilateral ptosis and forehead hirsutism (**c** and **d**).

Genitalia were hypoplastic. The patient had gross hypotonia and poor mimics. Heart and kidney ultrasonography scans were normal and brain MRI confirmed the hypoplasia of the corpus callosum. Inguinal hernias were surgically corrected at age 3 months. Recurrent obstructive apnoea associated with gastro-oesophageal reflux required multiple hospital admissions. Psychomotor development was severely impaired: he sat with support at 10 months of age and without support at 2 years of age. The first spoken words were observed at 3 years of age but non-verbal skills were less affected (non-verbal communication, imitative plays). There was no hearing loss.

At the last examination, at 4 years of age, he was 100 cm tall (M), weighed 18.4 kg (+2 SD) and had an OFC of 50 cm (−0.5 SD). The facial dysmorphism was quite the same as that recorded at the first examination but the forehead was more prominent and bulging, microretrognathia with overbite was more severe and the face was still hypomimic although no facial palsy was present. He was unable to walk. Neurological examination was otherwise unremarkable. His speech was limited to single, poorly understandable words.

Metabolic screening, creatine kinase and Steinert gene screening were normal. Systematic screening of subtelomeric regions disclosed a 14q deletion. No chromosomal rearrangement was found by FISH in the parents.

Patient 2 This boy was the first child of young healthy parents. Single thickening of nuchal skinfolds with increased translucency was found on ultrasonography at 12 weeks gestation. A karyotype, performed on amniotic fluid cells at 16 weeks of gestation, was considered normal (46,XY). The boy was delivered at 40 weeks gestation. Birth weight, length and OFC were 3.170 kg (10th centile), 50 cm (−1 SD) and 33.5 cm (−2 SD), respectively. Apgar score was normal. During the neonatal period, the boy was hypotonic and had coronal hypospadias, bilateral blepharophimosis and ptosis (surgically corrected at 10 months of age) and auricular septal defect, ostium secundum type. At age 6 months, he developed infantile spasms. Cortical atrophy and hypoplasia of the corpus callosum were evidenced on brain MRI. Blood karyotype and FISH for the Prader-Willi/Angelman region were normal. The boy was clinically re-evaluated at the age of 3 years. OFC and weight decreased by −2 and −1.5 SD, respectively, whereas height remained normal. Motor and mental developments were severely delayed. Facial dysmorphic features included hypertelorism, epicanthal folds, long palpebral fissures, bilateral ptosis, bushy eyebrows, long philtrum, tented upper lip, short neck and forehead hirsutism (Figure 1c and d). A multi-FISH analysis using a panel of subtelomeric probes was performed and led to the diagnosis of a cryptic terminal 14q deletion derived from a paternal cryptic t(14;17)(qter;qter)pat translocation (data not shown).

Methods

Molecular cytogenetics Chromosome analysis was performed on peripheral blood lymphocytes by G- and R-banding using standard and 550-band resolution technique. FISH was performed on metaphase spreads obtained using previously described cytogenetic techniques.[22] The terminal 14q deletion was diagnosed by subtelomeric FISH screening for both patients. The two deletions were further mapped by FISH with BAC and PAC probes chosen along the 14q arm from 97 Mb to the telomere (end: 106 368 585 bp). The relative order of those probes was obtained by the NCBI and Ensembl databases (http://www.ncbi.nlm.nih.gov/mapview/, http://ensembl.org/Homo_sapiens/cytoview).

The following BAC clone probes provided by M Rocchi (Uniba-Bari) were used: RP11-300N18, RP11-483K13, RP11-68I8, RP11-431B1, RP11-168L7, RP11-796G6, RP11-1017G21, RP11-356L8, RP11-456M14, RP11-454M12 and RP11-435F10 from centromere to telomere, respectively. The most distal PAC clone GS-820M16 was provided by Knight[23] (Table 2). DNA from BAC and PAC colonies was extracted using the Macherey-Nagel kit (Nucleobond, 74579, Hoerdt, France) and labelled with Cy3-dUTP

Table 2 FISH results with BAC and PAC probes

Chromosome 14 BACs/PACs	*Position (kbp)*	*NCBI end sequence*	*Ensembl*	*Patient 1*	*Patient 2*
RP11-300N18	93800–93944	AQ504718, AZ081941		Not del	—
RP11-483K13	95325–95535	AQ637174, AZ303373		Not del	—
RP11-68I8	97837–98010	AL163760.4	AL163760.4	Not del	—
RP11-431B1	98700–98770	AZ081948.2, AZ081949.2		Not del	—
RP11-168L7	100860–101046	AZ517793.1		Del	—
RP11-796G6	101187–101273	AQ500051.1	AL355032.6	Del	Not del
RP11-1017G21	101408–101600	AL118558.6	AL118558.6	—	Not del
RP11-356L8	101794–101966	AQ538229.1		—	Del
RP11-456M14	102088–102275	AQ582808		—	Del
RP11-454M12	102984–103176	AZ081843		—	Del
RP11-435F10	104816–104967	AZ081951.2		Del	Del
GS-820M16	〉106166–106288〈[a]		CTC-820M16	Del	Del

[a]Included in.

Table 3 Genotyping results with STS markers

STS		*Bp*	*Father*	*Patient 1*	*Mother*
D14S306	14q21.1	37398001–37398204	1 and 3	1 and 2	2 and 4
D14S77	14q24.2	72640306–72640535	1 and 3	3 and 4	2 and 4
D14S308	14q32.33	106175186–106175506	1	1	1
D14S1420	14q32.33	106209174–106209361	—	—	—
Primers 1[a]	Left	TGTTTGAAGAAGGGAGTCGT	1	2	2
	Right	CCCACTCCATGTCTTCTGTT	—	—	—
Primers 2[b]	Left	GTGCCTGTAGGTATCTATGC	1	2	2
	Right	GCTCCCTATTTGCAAGATAC	—	—	—

[a]Sequence 1.
[b]Sequence 2.

(Amersham Bioscience, PA53022, Gehealthcare, Europe Gmbh, Munich, Germany) by nick translation (Nick Translation System, 18160-010, Invitrogen, San Diego, CA, USA). The Cy3-labelled DNA probe was precipitated and hybridised using standard procedures. Twenty metaphases were analysed under a fluorescence DMRB microscope (Leica) equipped with Metasystem Isis software (Altlussheim, Germany).

Genotyping The DNA was extracted from peripheral blood lymphocytes using standard techniques for patient 1 and his parents. Genotyping of the DNA of the proband and his parents was performed by PCR amplification using STS microsatellite primers for STSs D14S306 (14q21.1), D14S77 (14q24.2), D14S308 (14q32.33) and D14S1420 (14q32.33). Two sequences (1 and 2) were tested for D14S1420 (Table 3). DNA was not available for patient 2 and his parents.

Results

Molecular cytogenetics

Patient 1 The deletion extended from a break point located between the undeleted clone RP11-431B1 and the deleted clone RP11-168L7 to the end of the chromosome 14q arm tagged by the most distal subtelomeric probe GS-820M16 (300 kb from the end of 14qter) (Table 2 and Figure 2a and b). The deleted segment was shown to be 6.55 ± 1.05 Mb long (Ensembl cytoview database).

FISH results' designation: .ish del(14)(q32.2→qter) (RP11-300N18+,RP11-483K13+,RP11-68I8+,RP11-431B1+,RP11-168L7-,RP11-796G6-,RP11-435F10-,GS-820M16-).

Patient 2 The deleted chromosome 14 was derived from a paternal cryptic translocation t(14;17)(q32.32;qter)pat. The deletion extended from a break point located between the undeleted clone RP11-1017G21 and the deleted clone RP11-356L8, to the distal part of 14q arm (clone GS-820M16) (Table 2 and Figure 2c–f). Its size was shown to be 4.67 ± 0.10 Mb long (Ensembl cytoview database).

FISH results' designation: .ish del(14)(q32.32→qter) (RP11-796G6+,RP11-1017G21+,RP11-356L8-,RP11-456M14-,RP11-454M12-,RP11-435F10-,GS-820M16-).

Genotyping

Patient 1 This patient had inherited a maternal and a paternal allele for STS D14S306 and D14S77, but STS D14S308 was uninformative. No paternal allele was observed for D14S1420 sequences 1 and 2 (Figure 3). This analysis showed that the deleted chromosome 14 was of paternal origin (Table 3).

Patient 2 No DNA was available for the second family but nevertheless the derivative der(14) was derived from a paternal translocation. Consequently, we assumed this deleted chromosome 14 to be of paternal origin.

Discussion

Deletions on chromosome 14q are usually associated with ring chromosome 14.[1,24] A purely distal 14q32 deletion was reported in less than 15 published cases (Table 1), and only 8 of them were analysed by molecular cytogenetics (Table 1). The deleted fragments were mapped in only four cases. Indeed Schlade-Bartusiak *et al*[20] described two patients with a terminal 14q32.3 deletion mapped by FISH using BAC clones. The first patient HSC1658 had a 3.2-Mb-long 14q32.3 terminal deletion with a proximal break point located between *CKB* and *KNS2* genes. The second patient HSC1363, also studied by Wintle *et al*,[12] had a 5.3-Mb-long 14q32.3 terminal deletion with a proximal break point located proximally to the deleted gene *DIO3*. Maurin *et al*[10] reported a third patient with a der(14)t(14;D/G)(q32.33;p12) resulting in a 1–1.6 Mb terminal 14q32.33 deletion with a break point located between non-deleted BAC RP11-1087P8 and deleted BAC RP11-417P24. Van Karnebeek *et al*[19] reported a fourth patient with a del(14)(q32.31) mapped by molecular analysis using PCR-based analysis of microsatellite repeat polymorphism[12,19,20] (Table 1). The deletion was shown to be truly

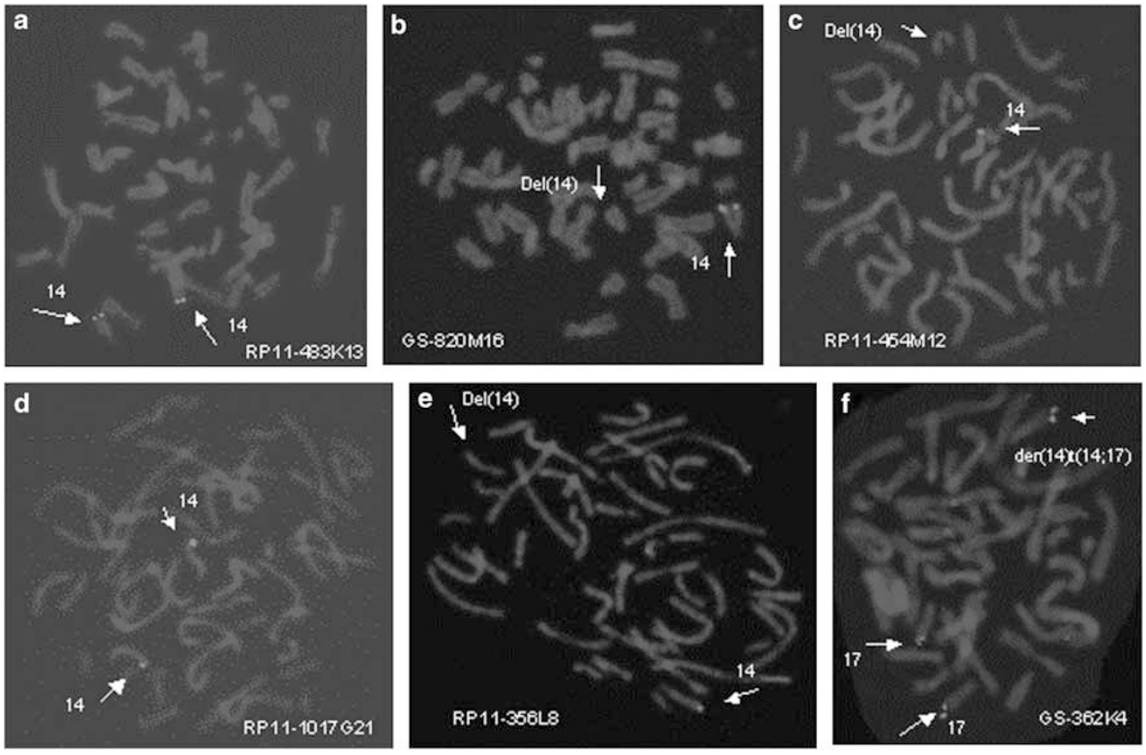

Figure 2 FISH using 14q32.3 BAC and PAC probes showed two red signals on chromosomes 14 when not deleted (probes RP11-483K13 (patient 1: **a**) and RP11-1017G21 (patient 2: **d**)) and a single red signal on its normal homologue when deleted for probes GS-820M16 (patient 1: **b**), RP11-454M12 (patient 2: **c**) and RP11-356L8 (patient 2: **e**). FISH using chromosome 17q subtelomeric probe GS-362K4 (patient 2: **f**) showed three signals on both normal 17 chromosomes and one on the der(14)t(14;17)(qter;qter).

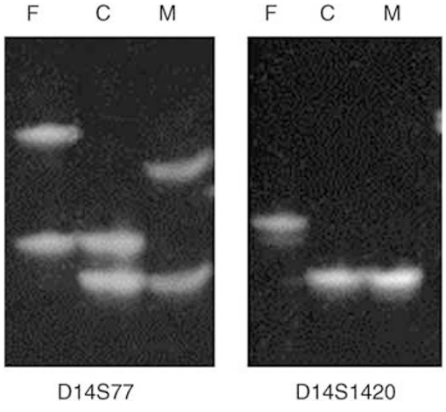

Figure 3 Migration pattern on the gels of amplified DNAs for patient no. 1 (C), his father (F) and mother (M) using microsatellite markers STS D14S77 and D14S1420 (sequence 1: left primer TGTTTGAAGAAGGGAGTCGT/right primer CCCACTCCATGTCTTC TGTT). The child inherited both paternal and maternal alleles for D14S77 and only maternal allele for D14S1420.

telomeric and the proximal break point was located between D14S985 (not deleted) and D14S292 (deleted).

We report here two cases: patient 1 with a pure del(14)(q32.2) 6.55 ± 1.05 Mb long, and patient 2 with a distal 14q32.32 deletion 4.67 ± 0.10 Mb long derived from a t(14;17)(q32.32;qter)pat. Considering this last patient, we must keep in mind that the features were partially related to the cryptic 17qtel duplication. The following features associated with 17q partial distal trisomy were previously elicited: psychomotor and growth retardation, microcephaly, high forehead and temporal retraction, narrow palpebral fissures, large mouth with thin lips, cleft palate, low hairline, malformed ears, webbed short neck, abnormal skeletal features and external genitalia.[25–27]

Regarding the phenotype associated with terminal 14q deletions among 23 cases of deletions distal to 14q24, Van Karnebeek *et al*[19] suggested to define the emerging phenotype by the features present in at least 50% of the cases such as neurologic deficits (mental retardation and hypotonia), a specific dysmorphic face (microcephaly, high and prominent forehead, blepharophimosis, epicanthi, broad and flat nasal bridge, short bulbous nose, broad philtrum, thin upper lip, small carpe-shaped mouth, highly arched palate, abnormal dentition, low-set ears with malformed helices and micrognathia) and a single palmar crease. Congenital malformations associated with such 14qter deletion were almost limited to congenital heart defects. Other rare anomalies were reported: haemangioma, coloboma, hypospadias, imperforate anus,

fingerlike thumbs and oesophageal atresia with tracheo-oesophageal fistula, hearing loss and cat cry.[19]

Compared to the clinical criteria suggested by Van Karnebeek *et al*,[19] on a cohort of deletions distal to 14q24, we found some discrepancies. Patient 1 was not microcephalic and both patients 1 and 2 had neither highly arched palate nor abnormal dentition. Prominent earlobes instead of thick helices, short neck and single palmar creases were noted in both our patients and had not been previously reported. These patients were suspected initially at prenatal ultrasound screening because of the presence of thick nuchal skinfolds. Interestingly, both had hypoplasia of the corpus callosum. Brain morphological investigations have been documented in 11 patients with pure or not 14q terminal deletion in the literature,[3,4,7–10,12,14,18,21] showing abnormalities in six patients. In one case, a subarachnoid haemorrhage over the cerebral convexity was observed at birth by CT scan, but the brain MRI was normal at 5 years of age.[8] In a second case, post-mortem examination showed irregular polygyria, lack of opercularisation of the temporal lobes, and occipital periventricular neuronal heterotopia.[7] In a third case, MRI showed non-specific white matter hyperdensity in the periventricular areas[10] and in a fourth case lissencephaly was reported.[21] An abnormal corpus callosum was disclosed only in the two following cases: (a) Mertens *et al*[18] reported a complete agenesis of the corpus callosum observed during autopsy of a newborn child associated with pure del(14)(q32)[18] and (b) Bregant *et al*[4] described a 2-week-old boy with asymmetric cranial lateral ventricles and hypoplastic corpus callosum associated with a der(14)t(10;14)(q24;q32)[4]. Unfortunately, the length of the deletion in the last two patients was not mapped as we did for our two patients with corpus callosum hypoplasia.

The delineation of a del(14)(q32) emerging phenotype is complicated by the fact that this region is submitted to imprinting. At least three imprinted genes have been reported in this region: *MEG3* and *DLK1* expressed maternally and paternally in humans, respectively [28] and the gene *DIO3* described as preferentially expressed from the paternal allele in the mouse fetus.[29] The three documented 14q32 deletion data reported two maternally[19,20] and one paternally[20] derived deletions. In the present observations, the loss of functionally active, paternally derived alleles, in combination with maternally imprinted genes, on 14q could be involved in the phenotype. Indeed patients 1 and 2 showed features observed in maternal uniparental disomy (UPD14) such as developmental deficiency, hypotonia, feeding problems and short stature. Patient 2 had a marked ptosis with long and narrow palbebral fissures. Interestingly, blepharophimosis was postulated to be characteristic for paternal UPD14,[30] but none of the three genes *MEG3*, *DLK1* and *DIO3* were deleted in this patient. Regarding patient 1, *DIO3* was deleted but it could not be assessed if *MEG3* or *DLK1* was deleted because these genes are located between the proximal and distal edge of the 14q32.2 break point: BACs RP11-431B1 (not deleted) and RP11-168L7 (deleted).

Conclusion

The number of reported cases with a terminal 14q32 deletion is very small. We report here two new cases with del(14)(q32.2) and del(14)(q32.32) of 6.55 ± 1.05 and 4.67 ± 0.10 Mb, respectively, both on the paternal chromosome 14. The patients had common postnatal features such as developmental deficiency, hypotonia, feeding problems, short stature, facial dysmorphic features and short webbed neck. We report two additional features that may help in prenatal diagnosis: thick nuchal skinfold and hypoplastic corpus callosum. Microcephaly usually reported in larger del(14q) was not present in our two patients. These findings should contribute to delineate the emerging phenotype in terminal 14q32 deletion but need further data.

Acknowledgements

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Electronic-database information

http://www.ncbi.nlm.nih.gov/mapview/; http://ensembl.org/Homo_sapiens/cytoview

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