

Delineation of 14q32.3 deletion syndrome

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Abstract

A patient with a 14q32.3 terminal band deletion and cat cry is reported. Review of four other 14q32.3 deletion cases suggests the possible presence of a recognisable 14q32.3 terminal deletion syndrome, which is characterised by (1) apparently postnatal onset of small head size in comparison to body size, (2) high forehead with lateral hypertrichosis, (3) epicanthic folds, (4) broad nasal bridge, (5) high arched palate, (6) single palmar crease, and (7) mild to moderate developmental delay. Although none of the above seven features is unique to this syndrome, and indeed are quite common in other chromosomal disorders or genetic syndromes, patients with a terminal 14q32.3 deletion do show a recognisable facial gestalt. Interestingly, unlike ring chromosome 14, the 14q32.3 terminal deletion has rarely been reported, possibly because it is harder to detect, and an optimal chromosome preparation is required for its identification.

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The occurrence of deletions of chromosome 14 is relatively rare. When detected, it can be an interstitial deletion with variable breakpoints and variable sizes,¹⁻⁵ or an apparently terminal deletion of variable size.⁶⁻⁷ The deleted chromosome 14 may also be present as a ring chromosome.⁸⁻⁹ To our knowledge, a deletion of the terminal band (14q32.3) with the breakpoint at 14q32.2 or 14q32.31 only has been reported in four previous cases.¹⁰⁻¹³

We present here a fifth case of an apparent 14q32.3 deletion with relatively few dysmorphic features and a history of cat cry during the first 2 months of life. A delineation of the 14q32.3 deletion syndrome is attempted.

Case report

The patient was a 3 year 9 month old Puerto Rican girl born at 34.5 weeks' gestation with a birth weight of 2580 g (75th centile) and a birth length of 47.5 cm (80th centile). The exact head measurement at birth was not available, but was reportedly in proportion to the body size. There was no history of mutagenic or teratogenic exposure, and the parents were in their early 20s at her birth. The mother's karyotype is 46,XX, but the father was unavailable for cytogenetic study. The family history is not further contributory and there is no consanguinity. According to the mother, during the first 2 months of life, the patient had "a



Figure 1 Patient at 3 years 9 months of age.

peculiar cry resembling a kitten's cry". The patient suffered from frequent respiratory infections in the first half of infancy requiring several admissions to hospital. A heart murmur reported at 1 year of age later disappeared spontaneously. Her developmental milestones were delayed. She crawled at 1 year, walked on her own at 2 years of age, and at 3 years 9 months she was not toilet trained and her speech was limited to a few simple words.

She presented as an amiable, cooperative child with apparent mental delay. Her height (97 cm) and weight (14.5 kg) were on the 25th centile, while her head circumference (47 cm) was on the 2nd centile. Bilateral epicanthic folds, high arched palate, left sided esotropia, and hypertrichosis on the lateral sides of the forehead (fig 1) were noted. The facial features were otherwise unremarkable, and her neck, chest, abdomen, and external genitalia were normal. She had a bridged transverse palmar crease on both hands, but no clinodactyly.

Materials, methods, and results

Laboratory studies showed plasma amino acids to be within normal limits. Karyotype analysis to investigate the possibility of a deletion of the distal short arm of chromosome 5 (cri du chat syndrome) was also performed. Peripheral lymphocytes were cultured for three to four days in RPMI 1640 + 12% FBS and antibiotics. Both chromosomes 5 appeared normal, but GTG banding showed a minute deletion of the terminal band of one chromosome 14 with the breakpoint at 14q32.2 or 14q32.31. The deletion was confirmed by high resolution analysis (fig 2), in which lymphocytes were cultured using a FUDR block:thymidine release at 17 and five hours respectively before harvest, and, again, no anomaly was detected in the short arm of either chromosome 5. FISH studies

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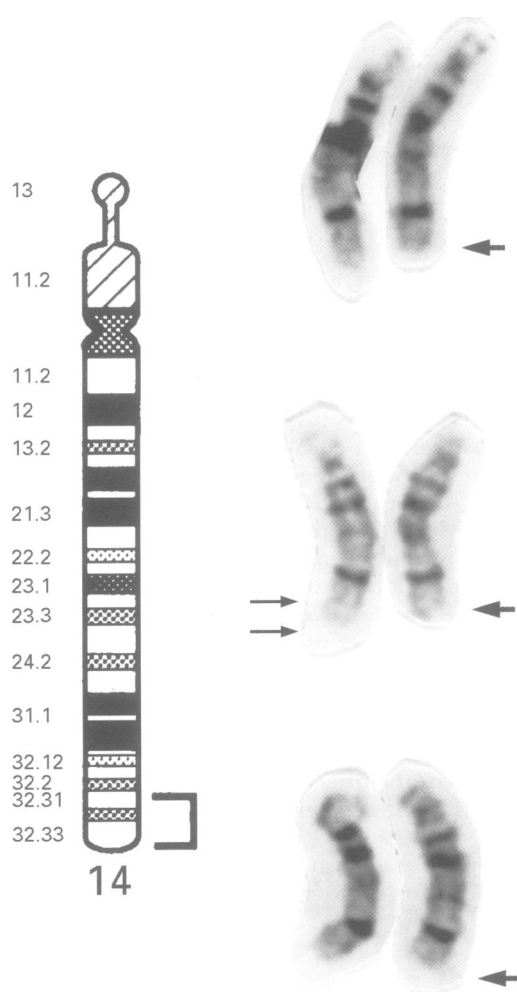


Figure 2 Chromosome 14 shown in ideogram and high resolution banding. The deletion is indicated by the bracket on the ideogram. In each banded pair, the breakpoint of the deletion is indicated by the single arrow on the right hand (deleted) chromosome. The extent of the deletion is indicated by the double arrows on the left hand (non-deleted) chromosome of the centre chromosome pair.

using a probe specific to the distal short arm of chromosome 5 (D5S23: 5p15.2, Oncor, Inc) hybridised to the distal short arm of both chromosomes 5 and failed to detect a submicroscopic deletion. However, FISH using two 14q

telomere specific probes (D14S308 and D14Z12: 14q32.3-qter, Oncor, Inc) confirmed the terminal 14q deletion. In 25 evaluable metaphases, 22 showed signal on one distal 14q only. The remaining three cells showed no signal within the metaphase indicating complete absence of hybridisation in those cells (within the limits of the probe as indicated by the manufacturer: 70-90% detection).

Discussion

The history of a kitten-like cry in the first 2 months of life prompted consideration of a diagnosis of 5p deletion syndrome in our patient, although apart from her borderline microcephaly and residual epicanthic folds, she does not have any other facial features of cri du chat syndrome. Furthermore, her normal height and weight are also unusual for 5p deletion syndrome. Karyotype analysis showed no obvious deletion on the short arm of either chromosome 5, but instead a subtle deletion of the terminal band of the long arm of one chromosome 14 was noted. To ensure that a small 5p deletion or rearrangement was not overlooked, a high resolution analysis and FISH using a cri du chat 5p site specific probe were also performed. Both studies were negative for 5p anomalies, but the small deletion of the terminal band of 14q was verified by cytogenetics and FISH. Thus, our patient has an apparently terminal 14q32.3 deletion with history of cat cry in early infancy.

Cat cry is evidently not pathognomonic for 5p deletion syndrome. Other chromosomal aberrations, such as an 8p duplication¹⁴ and the current example of a terminal band deletion of 14q, are also associated with cat cry in infancy. The pathogenesis of cat cry has not been fully elucidated. Early belief that laryngeal abnormalities were the cause has not been substantiated, since although variable laryngeal anomalies may be found, some patients may not have any laryngeal anomaly at all.¹⁵ A possible causal component from the central nervous system has also been entertained.¹⁶ In nearly all instances, the cat cry is not a permanent phenomenon, usually disappearing after the third month of age.

Table 1 Pertinent clinical features of five patients with a 14q32.3 deletion

	Hreidarsson and Stamberg ^{10*}	Telford et al ¹¹	Wang and Allanson ¹²	Wintle et al ¹³ (case 3)	Present case
Age	12 y	2 y 2 mth	3 y 3 mth	2 y	3 y 9 mth
Height (centile)	<3rd	75th	10th	90th	25th
Weight (centile)	5th	75th	3rd	75th	25th
Head size	50th	25th	5th	25th	2nd
Development	Verbal: 94 Performance: 78	Moderate deficit	Slow language development	Moderate global developmental delay ? (-)	Moderate global developmental delay
High forehead	+	+	+	?	+
Lateral forehead hypertrichosis	?	+	+	? (-)	+
Broad nasal bridge	+	+	+	? (-)	+
High arched palate	+	+	+	+	+
Epicanthic folds	?	+	+	Blepharophimosis and ptosis	+
Single palmar crease	-	?	+	+	+
History of hypotonia	-	+	-	+	-
Clinodactyly	-	-	+	-	-
Other eye anomalies	-	Ptosis	Left optic nerve coloboma	Ptosis	Left esotropia
Congenital heart disease	+	-	-	-	-
Seizures	-	-	-	-	-
Chromosome breakpoint	14q?32.3*	14q32.3	14q32.2	14q32.3	14q32.31

*Probably not a terminal deletion, see case 2 of Wintle et al.¹³

Review of published reports showed 14qter deletions as a result of ring chromosomes as well as four previously published cases with supposedly terminal 14q32.3 deletions.¹⁰⁻¹³ In an additional fifth terminal deletion case,⁷ the patient was reportedly a mosaic with 64% of the peripheral blood cells showing del(14)(q32.3). However, this patient has significantly more abnormal clinical findings than the other 14q32.3 deletion cases, and the published ideogram and the partial karyotype suggested a breakpoint at 14q32.1 rather than at 14q32.3. Therefore, this case was not included in our comparison.

The clinical features of the four terminal 14q32.3 deletion cases and of our own case are listed in table 1. It is apparent that the case of Hreidarsson and Stamberg¹⁰ is different from ours and the other three cases,¹¹⁻¹³ especially with regard to the head circumference and mental status. In fact, the case of Hreidarsson and Stamberg¹⁰ is apparently not a simple 14q terminal deletion by DNA analysis, but is probably an undetected interstitial deletion or a cryptic translocation (reinvestigated as case 2 in Wintle *et al*¹³). There is similarity in some clinical features with the other cases suggesting a possible overlap of the deleted region, but because this case does not fit the criteria of being a true terminal 14q deletion, it was not used in the final syndrome delineation.

The remaining four cases have in common a significant number of features suggesting a 14qter deletion syndrome. Our own patient and the cases of Wang and Allanson¹² and Telford *et al*¹¹ are quite similar clinically, showing: (1) apparently postnatal onset of relatively small head size in comparison to body size, (2) high forehead with lateral hypertrichosis, (3) broad nasal bridge, either prominent or flat, (4) high arched palate, (5) residual or apparent epicanthic folds, (6) a single palmar crease, and (7) mild to moderate developmental delay. Nonetheless, only the high forehead with lateral hypertrichosis may be unique for this deletion syndrome. The other dysmorphic features singly or in combination are quite common clinical findings. In the final case, Wintle *et al*,¹³ case 3, which was defined as a terminal deletion by both cytogenetic and molecular studies, several of the clinical features, such as the well documented postnatal onset of relatively small head size, moderate global developmental delay, high arched palate, and single transverse palmar crease, are compatible with those found in the other three cases. However, the severe ptosis/blepharophimosis is unique here, and there is no mention of a high forehead with lateral hypertrichosis. This phenotypic variation may be the result of a slightly different deletion breakpoint or may be the result of other factors in this patient unrelated to the 14qter deletion.

It is interesting to note that most of the ring chromosome 14 cases, especially those with minimal deletion of terminal 14q,¹⁷ do have similar facial features as described above for the 14q32.3 deletion cases. This clearly supports the delineation of 14q32.3 terminal deletion syndrome, since a ring chromosome

14 with a small distal long arm deletion should be analogous to a small terminal deletion of 14q. In a ring chromosome formation of an acrocentric chromosome, the concurrent deletion of the p arm has never been shown to contribute any phenotypic effect. Interestingly, seizure disorder and retinal anomalies appear to be prevalent in ring 14 cases. Perhaps the mosaicism usually associated with instability of a ring chromosome giving rise to cells with either double sized ring chromosomes (that is, duplication of 14¹⁸) or loss of the ring chromosome (that is, monosomy 14¹⁷) could account for the more severe clinical manifestations. Furthermore, there have been more ring chromosome 14 cases reported than 14q32.3 deletion cases. In terms of cytogenetic analysis, it is easier to identify a ring chromosome than to detect a subtle q arm deletion.

In conclusion, the comparison of four patients with a terminal 14q32.3 deletion suggests the presence of seven aforementioned common clinical features and a recognisable facial gestalt.

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