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Terminal 22q deletion associated with a partial deficiency of arylsulphatase A

K Narahara, Y Takahashi, M Murakami, K Tsuji, Y Yokoyama, R Murakami, S Ninomiya, Y Seino

Abstract

A 7 month old girl with psychomotor retardation, hypotonia, and minor malformations was found to have a terminal deletion of the long arm of chromosome 22, del(22)(q13.31). The partial deficiency of arylsulphatase A (ARSA) and the normal level of NADH diaphorase 1 (DIA1) suggests that the ARSA locus can be regionally assigned to 22q13.31→qter and the DIA1 locus can be excluded from the same segment. This report is the third published case with a terminal 22q deletion.

Partial monosomy 22 has been reported in relatively few cases. Most of them have an r(22), and there have been only two instances of a terminal deletion of the long arm.[1 2] We describe here another patient with a terminal 22q deletion. Gene dosage studies of arylsulphatase A (ARSA) and diaphorase 1 (DIA1) supported their localisations on the distal long arm of chromosome 22.

Case report

A female patient was seen when she was 7 months old. She was the third child of 26 year old parents. There was no family history of miscarriage or multiple congenital anomalies. Her parents and two older sibs were healthy. The pregnancy and delivery were uneventful. Birth weight was 3020 g (50th centile), length 50·5 cm (50th centile), and head circumference (OFC) 33·0 cm (30th centile). At the age of 2 months, the infant was admitted to hospital because of failure to thrive, congenital stridor, and hypotonia. Laboratory studies, including urine analysis, complete blood counts, serum creatine kinase, blood lactate and amino acid levels, electroencephalography, electromyography, and cranial CT scan, showed normal results. An indwelling nasogastric tube was placed because of poor feeding. At 3 and 6 months of age, respectively, the infant was admitted to hospital because of bacterial pneumonia. Physical examination at the age of 7 months showed a floppy infant with a few minor malformations (fig 1). The patient weighed 6800 g (10th centile), was 70·5 cm long (50th centile), and had an OFC of 43·0 cm (30th centile). The head was plagiocephalic with a flat left occiput. The eyes were almond shaped and deeply set and the palpebral fissures slanted slightly upwards. The ears were rather large. There were also full eyebrows, micrognathia, high arched palate, and subcutaneous syndactyly between the second and third toes.

The subsequent clinical course was marked by profound psychomotor retardation and several episodes of lower respiratory tract infections. At 2 years of age, the patient's developmental quotient was 25% that of a child of the same age. The patient's weight was 9205 g (3rd centile), height was 85·0 cm (50th centile), and her OFC was 46·3 cm (30th centile). She died suddenly at $2\frac{1}{2}$ years of age. Permission for necropsy was not granted.

High resolution GTG banding analysis of cultured lymphocytes and skin fibroblasts showed a terminal deletion of the long arm of chromosome 22 in all cells examined (fig 2). Her karyotype was designated 46,XX,del(22)(pter→q13.31:). The parents had normal chromosomes. Unfortunately, a cell line is not available from this patient.

NADH diaphorase activity of red blood cells (DIA1) was measured using the method of Hegesh *et al*,[3] and arylsulphatase A (ARSA) activity in leucocytes was assayed using the method of Galjaard.[4] The DIA1 level was normal (2·59 μmol/min/g Hb, 104% of the normal value), while the ARSA activity was reduced (51 nmol/h/mg protein, 52% of the normal and 42% of the mean parental value).

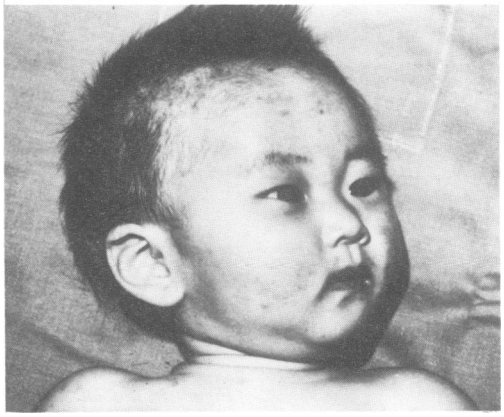

Figure 1 The proband aged 7 months

Department of Pediatrics, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama 700, Japan.
K Narahara
Y Takahashi
M Murakami
K Tsuji
Y Yokoyama
R Murakami
S Ninomiya
Y Seino

Correspondence to Dr Narahara.

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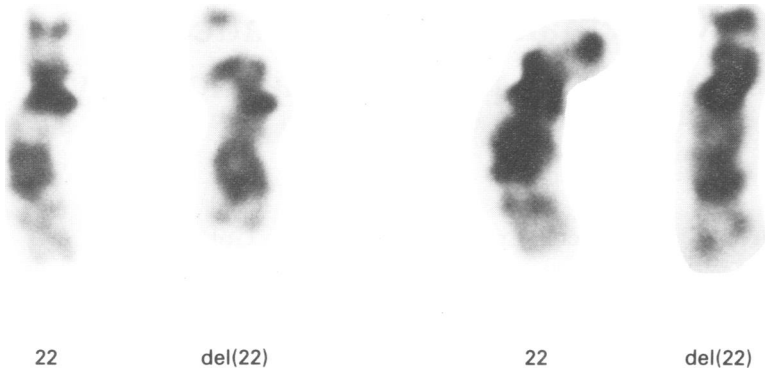

Figure 2 Partial karyotype of the proband

The results are compatible with hemizygous deficiency of the ARSA locus in the patient.

Discussion

This is the third published case of a patient with a terminal deletion of the long arm of chromosome 22. The first patient had both monosomy for 22q12→qter and trisomy for 22p11→pter, resulting from a recombination of a maternal pericentric inversion of chromosome 22, inv(22)(p11q12).[1] In this patient, however, the breakpoint on the long arm of chromosome 22 is more likely to be in 22q13. The second patient had de novo monosomy for 22q13.31→qter.[2] This patient was ascertained because of multiple congenital anomalies, mental retardation, and, interestingly, the Goldenhar complex.

Clinical findings in the reported cases with a terminal deletion of 22q and those with r(22).

	Watt *et al*[1]	Herman *et al*[2]	Present case	Cases with r(22)[5] (%)
Age at examination	14 y	Newborn	7 mth	
Sex	M	M	F	16M/18F
Birth weight (g)	ND	3105	3020	2960
Developmental delay	+	+	+	90
Poor weight gain	ND	ND	+	29
Short stature	+	ND	−	17
Hypotonia	−	ND	+	75
Unsteady gait	+	/	/	87
EEG abnormality	−	+	−	50
Microcephaly	−	Macro	−	41
Epicanthic folds	+	−	−	86
Full eyebrows	+	−	+	100
Deep set eyes	+	−	+	
Large ears	+	−	+	73
Abnormal ears	+	+	−	85
Micrognathia	−	−	+	28
High arched palate	−	+	+	42
Dental malocclusion	+	/	/	54
Thick lips	−	−	−	77
Syndactyly of toes	+	−	+	60
Clinodactyly	+	−	−	32

The table summarises the clinical findings in these three patients together with findings for patients with a ring chromosome 22 for phenotypic comparison. In the patients with terminal 22q deletions, mental retardation was the only common finding. In the patients with r(22) who also had monosomy for distal 22q, there were no consistent features except for non-specific abnormalities such as mental retardation, hypotonia, epicanthic folds, full eyebrows, ear malformations, thick lips, and syndactyly.[5] While deletions of proximal 22q are associated with the DiGeorge syndrome,[6] deletions of distal 22q may not produce any distinctive phenotype.

Both the ARSA and DIA1 loci have been assigned to 22q13.31→qter (HGM10).[7] The results of gene dosage studies in our patient indicate that the ARSA locus can be mapped regionally to 22q13.31→qter, and that the shortest overlapping region with the DIA1 locus can be narrowed to 22q13.31. Partial deficiency of ARSA is known to be associated with metachromatic leucodystrophy. The existence of a patient with a deleted r(22) who later had progressive polyneuropathy[8] emphasises the importance of an ARSA assay in the clinical evaluation of patients with distal 22q monosomy.

Another prominent finding in the present patient is marked axial hypotonia, a feature also characteristic of the patients with r(22). The myoglobin locus (*MB*) has been mapped to the long arm of chromosome 22, 22q11.2→q13 (HGM10).[7] It remains to be determined whether the marked hypotonia is the result of a hemizygous deficiency of the MB locus or of some locus crucial to cerebellar embryogenesis.

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