

# Amelia, dextrocardia, asplenia, and congenital short bowel in deleted ring chromosome 4

J W Hou, T R Wang

## Abstract

We report a female baby with multiple congenital anomalies including left upper amelia, congenital short bowel with malrotation and pseudo-obstruction, dextrocardia with situs solitus, patent ductus arteriosus, and a tiny atrophic spleen. Chromosome study showed *de novo* 46,XX/46,XX,-4,+r(4)(p16→q22.3)/47,XX,4,+r(4)(p16→q22.3),+del(4)(pter→q22.3). The clinical findings in the patient were probably caused by the interaction of partial trisomy 4pter→q22.3 or 4p16→q22.3 and partial monosomy of 4q22.3→4qter. This karyotype and pheno-

type have not previously been reported.

(J Med Genet 1996;33:879-881)

Key words: amelia; congenital short bowel; chromosome 4.

Limb deficiency defects are relatively rare, particularly in chromosomal aberrations such as segmental autosomal monosomies or trisomies. The occurrence of ectrodactyly or its equivalents in patients with del(4q) and r(4) in several cases<sup>1</sup> suggested that the genes related to limb deficiency may be assigned to the tips of 4p and 4q.<sup>1</sup> We describe a patient with congenital short bowel with midgut malrotation and pseudo-obstruction, dextrocardia, and dysplastic spleen as well as amelia, as a result of del r(4) mosaicism.

## Case report

The female patient was the first child of unrelated, healthy Chinese parents. Birth weight was 3500 g, length 50 cm, and OFC 33.5 cm (all were normal for a term Chinese female baby). The perinatal history was uneventful. Her mother denied any history of smoking, alcohol, drug or radiation exposure, and the procedures of chorionic villus sampling or amniocentesis. Ultrasonography at 25 weeks' gestation showed dilated bowel, but limb anomalies could not be detected. The amount of amniotic fluid was normal and no amniotic bands were visible. The mother was referred to our hospital with the suspicion of gastrointestinal obstruction in the fetus.

After birth, the baby was noted to have good activity. No significant head deformity or facial dysmorphism, except for naevus flammeus over the forehead, was noted. The musculature of the chest was normal but the apical impulse of the heart was located on the right side. No murmur was heard. The liver was palpable 1 cm below the right costal margin at the midclavicular line. The tip of the spleen was not palpable. Absence of the whole left upper extremity was the most significant finding (fig 1).

Abdominal distension with bile stained vomit developed gradually during the first 24 hours of life although normal meconium passage was noted. Radiographs showed suspected triple bubble sign as well as dextrocardia, left acheiria, and hypoplasia of the left scapula (fig 2A). Laparotomy was performed on the second day because of the progressive course of intestinal obstruction. Haemogram, liver enzymes, acid base, and electrolytes were all normal. The operative findings showed dila-

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Received 6 December 1995  
Revised version accepted for publication 21 March 1996



Figure 1 The patient at 1 week of age, showing total absence of the left upper extremity. The transverse abdominal scar is from a previous laparotomy. (Photograph reproduced with parental consent.)

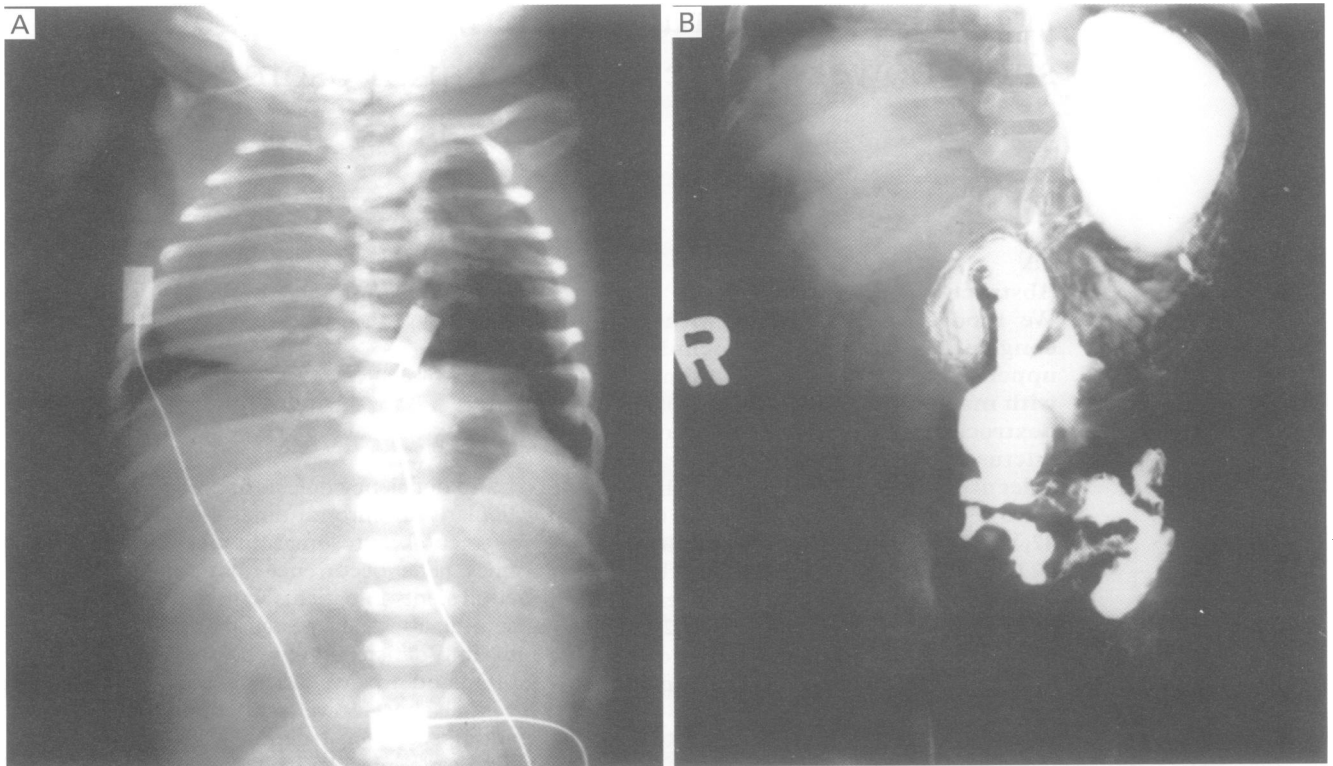


Figure 2 Radiographs of the patient showing (A) triple bubble bowel sign (note dextrocardia, hypoplastic left scapula, and total absence of the left upper extremity at 1 day), (B) short bowel with segmental dilatation below the duodenum with malrotation by contrast study at 40 days. Gastro-oesophageal reflux was also noted.

tation of the fourth portion of the duodenum and upper jejunum (the dilated part was 15 cm in length and 4 cm in diameter) and only a residual terminal ileum of about 15 cm from the level of the obstruction to the ileocaecal valve. No evidence of pyloric hypertrophy was noted. The colon was normal. The upper gastrointestinal series also showed short bowel with segmental dilatation below the duodenum with midgut malrotation (fig 2B). Congenital short bowel with pseudo-obstruction was diagnosed. The spleen was abnormal with only a  $1 \times 1$  cm infarcted section of spleen present. Resection of the dilated part of bowel loop, subsequent end to end anastomosis, and excision of the atrophic accessory spleen were

performed without complications. Histopathology of the resected intestine showed diffuse congestion and oedematous changes with inflammatory cell infiltration. Ganglion cells and nerve bundles were present throughout the whole intestinal segment. The structure of villi was intact.

Dextrocardia with situs solitus, patent ductus arteriosus, and incomplete patent foramen ovale with a left to right shunt were documented by echocardiography. Sonographs of the brain, liver, and kidneys were all negative. Liver scan with Tc-99m phytate showed no spleen uptake shadow postoperatively. Chromosome study from the peripheral lymphocytes stimulated by phytohaemagglutinin of the patient showed  $46,XX/46,XX,4,+r(4)(p16 \rightarrow q22.3)/47,XX,-4,+r(4)(p16 \rightarrow q22.3),+del(4)(pter \rightarrow q22.3)$  in a ratio of 84%/12%/4% (fig 3). The karyotypes of both parents were normal.

The postoperative course was smooth and total parenteral nutrition (TPN) was given. Contrast study with urographin showed patency but poor peristalsis of the anastomotic intestine at 9 days of age. Incremental enteral feeding was tried from 12 days. There was often vomiting without bile and large residual gastric volume. Oesophagogram showed moderate gastro-oesophageal reflux. The emptying time from upper oesophagus to rectum was about three hours, which is within normal limits for 44 days of age. The gastric half emptying time following administration of a test meal labelled with 2 mCi of Tc-99m sulphur colloid was 96.15 minutes (normal  $66 \pm 32$  minutes). The patient was discharged at 62 days old. Home TPN was started. Frequent bile stained

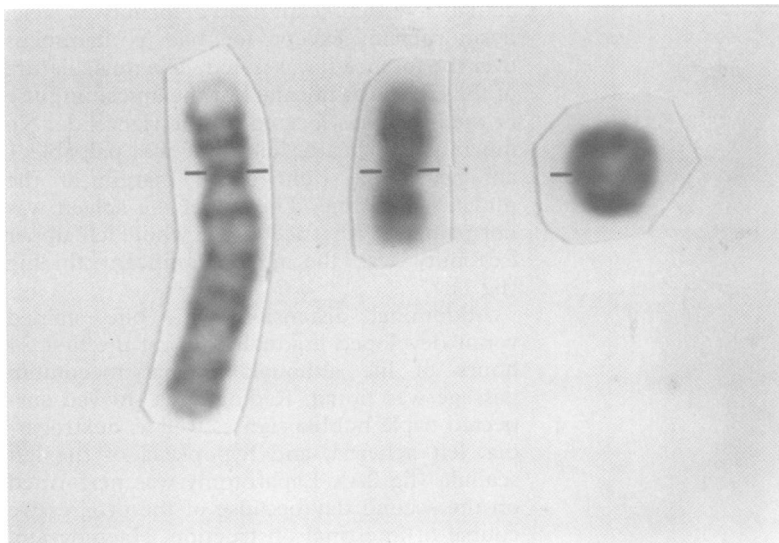


Figure 3 Partial karyotype by G banding of the proband's normal and abnormal chromosomes 4 with a deleted ring form.

vomiting after enteral feeding occurred, even with the use of antiemetics, in the following six months.

### Discussion

The formation of limbs in the fetus can be suppressed by genetic or environmental factors. Thalidomide, an anti-nauseant, has been established to cause a characteristic syndrome of malformations,<sup>2</sup> consisting of absence or gross deformities of the long bones, intestinal atresia, and cardiac anomalies. This cause was easily excluded by negative maternal drug (particularly antiemetics) exposure during pregnancy. Other causes of fetal limb deficiency defect (LDD) include chorionic villus sampling (CVS),<sup>3</sup> amniotic band sequence,<sup>4</sup> teratogen exposure,<sup>5</sup> or a vascular accident.<sup>4,5</sup> CVS was not performed in this case. There was also no evidence of amniotic bands or exposure to irradiation, vasoactive drugs, or smoking during pregnancy.

The most extreme form of abnormality of the extremities is total absence (amelia); this is rare and may be associated with other non-limb malformations owing to mendelian inheritance or chromosomal aberrations.<sup>4</sup> The recognition of the cytogenetic basis of LDD is of importance because it may influence the individual prognosis and genetic counselling. Disturbed development of the limb buds has been mentioned in cases with ring chromosome 4 and deletions in 4q33, 4q, 7q21.3 q22.1, 2q31, and 6q21.<sup>1</sup> Thus, chromosome study is recommended in cases with LDD.

Congenital short bowel syndrome has rarely been reported since the first case report in 1969.<sup>6</sup> This syndrome is usually associated with malrotation and clinical features similar to those following massive intestinal resection.<sup>7</sup> It is quite different from another syndrome of congenital short intestine in association with pyloric hypertrophy and malrotation. The latter is the result of an absence or diminution of argyrophil ganglion cells in the small intestine wall.<sup>8</sup> Dextrocardia with normal situs is much less often seen than dextrocardia with total or partial situs inversus.<sup>9</sup> Dextrocardia is caused by formation of the cardiac loop to the left instead of to the right. This case is the first report of such cytogenetic changes associated with both congenital short bowel syndrome and dextrocardia with situs solitus.

The complexity of the chromosome 4 rearrangements in this case could explain the phenotypic spectrum involving multiple organs. The genetic interactions include different aneuploid segments: monosomy 4q22.3→qter, trisomy 4pter→q22.3, and deletion of the tips of 4p in the ring form. The generation of mosaic aneuploid cells during embryogenesis influences the rate of proliferation and differentiation and has a pronounced effect on the organisation of certain structures, especially vascular disruption in the territories of major arteries for left upper limb budding, midgut elongation, spleen formation, and cardiac loop orientation.<sup>4,5</sup> Ivemark syndrome, a rare disorder of asplenia-cardiovascular anomalies, has been described as a single gene disorder (autosomal recessive inheritance).<sup>10</sup> The present case indicates that one gene or the gene whose mutation can cause Ivemark syndrome may be on chromosome 4.

Short bowel syndrome encompasses a spectrum of metabolic and physiological disturbances<sup>7</sup> resulting from massive anatomical or functional diminution of the small bowel in this patient. Home parenteral feeding may allow long term survival, but the prognosis in this case will be not good because of the susceptibility to infection because of asplenia.

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