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Diaphragmatic herniae and translocations involving 8q22 in two patients

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Abstract

Two girls with congenital diaphragmatic herniae are reported. Both were discovered to have a balanced reciprocal translocation involving 8q22.3. In one girl the translocation was de novo, in the other it was maternally inherited. Uniparental disomy was excluded in both. 8q22.3 may be the location of a gene affecting development of the diaphragm.

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Congenital diaphragmatic hernia (DH), in which abdominal organs protrude into the thoracic cavity, arises because of abnormal development of the diaphragm. The diaphragm normally develops from four different embryological structures, the septum transversum, the oesophageal mesentery, the pleuroperitoneal membrane, and the body wall. The septum transversum makes up the majority of the diaphragm and is mesodermal in origin. The diaphragm is formed by 8 weeks of gestation. Primary failure of the septum transversum to grow is thought to result in most types of diaphragmatic herniae, including the most common type to present in the neonatal period, the posterolateral or Bochdaleck hernia. Other types, classified by the location of the defect, include the anterolateral hernia, the hiatus hernia occurring through an abnormally large oesophageal opening, and the parasternal or Morgagni hernia. The latter hernia is thought to have a different embryological cause and results from failure of development at the costal and sternal origin of the peripheral musculature.

The incidence is difficult to ascertain as a significant number of affected babies die at birth. A live birth incidence between 1 in 4000 and 1 in 10 000 has been estimated.[1] The aetiology of this developmental defect is unknown. DH are increasingly being picked up prenatally on routine ultrasound scan but the mortality is at least 50%. Familial cases have been described, although most are sporadic. Multifactorial inheritance seems most likely.[2]

We present two girls who survived with diaphragmatic hernia and who were both found to have a balanced reciprocal translocation involving a breakpoint at 8q22.

Case reports

CASE 1

Case 1 (laboratory reference no 92/3725) was the first child of unrelated white parents. On routine ultrasound scan at 20 weeks' gestation it was shown that she had a left sided diaphragmatic hernia. No other structural abnormalities were shown. The pregnancy was otherwise normal. She was born by emergency caesarian section at 37 weeks. Birth weight was 2560 g.

Surgery to correct the posterolateral diaphragmatic hernia was successful and she has since progressed normally. She sat at 8 months and was crawling by 13 months. A developmental assessment at 27 months showed her to have mild delay. Her development was assessed at a 23 month level. On physical examination her height was on the 10th centile, weight on the 3rd centile, and head circumference on the 25th centile. She was not dysmorphic. Feeding was still a problem but she was generally healthy.

A karyotype performed in utero showed case 1 to have a balanced reciprocal 8;13 translocation and an identical translocation was found in her mother. The karyotype of case 1 was therefore 46,XX,t(8;13)(q22.3;q22)mat (figs 1 and 2). Her father had normal chromosomes. Other family members were not tested. The mother was clinically normal but did not undergo further investigations.

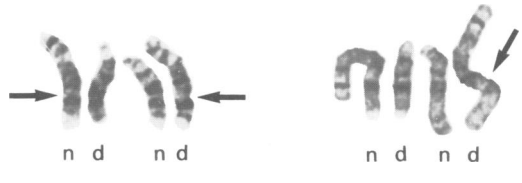

Figure 1 Partial G banded karyotypes showing the areas of homology between the normal (n) and derived (d) chromosomes. The left hand set is from the mother of case 1 who has the 8;13 translocation and the right hand set from case 2 who has the 8;15 translocation. Each set from left to right: the normal 8, the derived D group chromosome, the normal D group chromosome, and the derived chromosome 8. Arrows indicate the common breakpoint at 8q22.3.

CASE 2

Case 2 (laboratory reference no 91/2690) was born after a normal pregnancy at 37 weeks. She was the second child born to non-consanguineous white parents. The delivery was normal and her birth weight was 2860 g. Soon after birth she became tachypnoeic and blue and was intubated at $1\frac{1}{2}$ hours. A right sided posterolateral diaphragmatic hernia was diagnosed. She was transferred to the Regional Surgical Unit and was operated on at 2 weeks of age. She was ventilated for a further two weeks. Oesophageal reflux was a continual problem. A repair of the diaphragmatic hernia was necessary at 6 months of age.

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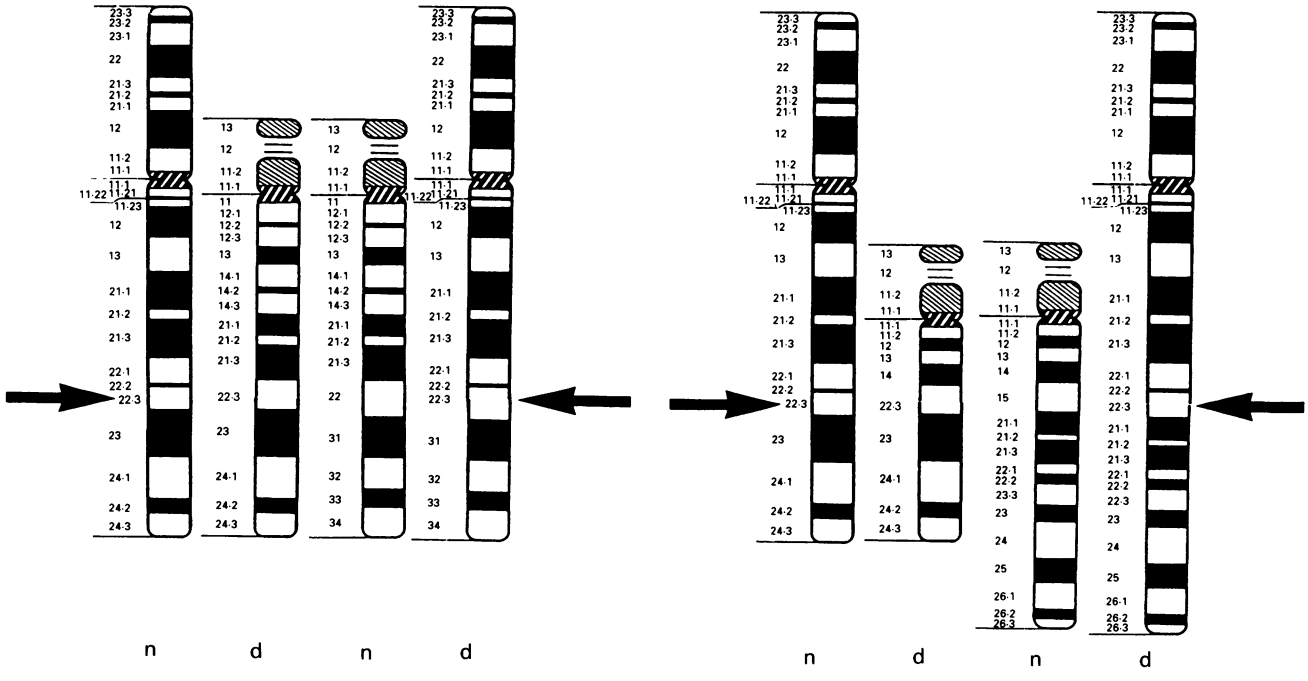

Figure 2 Idiograms of the same sets of chromosomes arranged in the same order as fig 1.

At 7 months of age she was progressing well. She was sitting with support and was responsive. On examination her height, weight, and head circumference were just below the 3rd centile. She had normal hair. Her palpebral fissures were minimally upward slanting but there were no other dysmorphic features. She has progressed well and her length and weight by 14 months are on the 10th centile.

A karyotype showed her to have a balanced reciprocal 8;15 translocation; both her parents had normal chromosomes and the karyotype of case 2 is therefore 46,XX,t(8;15)(q22.3; q15)de novo (figs 1 and 2).

MOLECULAR GENETIC ANALYSIS

To exclude the possibility of uniparental disomy, the parental origin of the chromosomes involved in the translocations was determined by the amplification of DNA microsatellite repeats[3] using PCR. Primer sequences included LPL3GT (at the lipoprotein lipase locus on 8p) and Mfd 169 (D8S198),[4] MIT-MS178(D15S101), MIT-MS112(D15S98), MIT-MS34(D13S115),[5] and AFM155yb6 (D13S159).[6] PCR conditions were those described by Hudson *et al.*[5]

In each case, uniparental disomy was excluded by the presence of both maternal and paternal alleles for the translocated chromosomes.

Discussion

Both girls reported here have a unilateral posterolateral diaphragmatic hernia and a reciprocal translocation involving a breakpoint at 8q22.3. In case 2 the translocation was de novo but in case 1 it was maternally inherited. Neither girl has any other significant morphological abnormalities although case 1 shows mild developmental delay. Although this chromosome finding may be a chance event it may also point to a putative gene at 8q22.3 which affects development of the diaphragm. The increased risk of uniparental disomy in translocation carriers led us to exclude this as a possible mechanism in these two children.

No gene has yet been mapped within the subband 8q22.3 and only the avian myeloblastosis viral (V-myb) oncogene homologue like 1 gene (MYB4) has been mapped as precisely as 8q22.[7] Genes with broader map locations which overlap with 8q22 include the calbindin 1 gene (CABB1, 8q21.3→q22.1), two steroid 11 β-hydroxylases of the cytochrome P450 subfamily X1B (CYB11B1+polypeptide 1 and CYP1132+polypeptide 2, both within 8q21→q22), and the cell surface associated heparan sulphate proteoglycan 1 gene (HSPG1 at 8q22→q24). None of these is an obvious candidate gene for DH.

DH has previously been reported in association with chromosome abnormalities which include an interstitial deletion of chromosome 1 (q32→q42),[8] mosaic tetrasomy 12p,[9] ring chromosome 4, and trisomies for chromosomes 13, 18, and 21.[10] However, in all these cases, DH is one of a spectrum of anomalies; by contrast isolated DH has not previously been associated with any cytogenetic abnormality. An increasing number of genes have been mapped by virtue of their association with chromosomal translocations; Human Gene Mapping 11 lists 28 conditions mapped in this way to the autosomes and 14 conditions mapped to the X chromosome.[11] Thus, in the present case, we propose that a gene involved in the development of the diaphragm or its constituents may map to the 8q22.3 sub-band.

We encourage other clinicians to karyotype further cases of isolated diaphragmatic hernia with particular reference to band 8q22.3.

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