A mild phenotype associated with der(9)t(3;9) (p25;p23)

R J McClure, N Telford, S J Newell

Department of Paediatrics and Child Health, St James's University Hospital, Leeds LS9 7TF, UK
R J McClure
S J Newell

Department of Cytogenetics, St James's University Hospital, Leeds LS9 7TF, UK
N Telford

Correspondence to: Mr Telford.

Received 24 August 1995
Revised version accepted for publication 5 February 1996

Abstract
A female infant is described with hypoglycaemia, hypotonia, obesity of the trunk and thighs, and mild dysmorphic features. Growth parameters were consistently above the 90th centile. Chromosome analysis showed her to have a derived chromosome 9 inherited from a maternal t(3;9)(p25;p23) by adjacent I segregation. She had features in common with both the dup(3p) and del(9p) syndromes. There are few reports of this chromosome rearrangement and the features are milder than expected for the degree of imbalance, complicated in males by sex reversal. The repeated reports of macrosomia may suggest an overgrowth syndrome.
(J Med Genet 1996;33:625-627)

Key words: chromosome abnormalities; phenotype-karyotype correlation; del(9p); dup(3p).

Duplications and deletions of chromosome segments can arise as a result of the segregation of a parental balanced rearrangement, such as a reciprocal translocation. Usually inheritance of the unbalanced form of a translocation leads to significant congenital abnormalities. Such patients manifest phenotypic features of chromosome imbalance syndromes. Careful study of the genotypic defect and the resultant phenotype allows inference about the genetic content of the affected portion of the chromosome. We report an infant who has a duplication of chromosome 3p25-pter and a deletion of 9p23-pter by inheritance of a derived chromosome 9 from a (3;9)(p25;p23) maternal translocation. There has been one other published report of a female of similar age¹ (table) and a further case of a 26 year old male with sex reversal.² The proband was the second daughter of healthy, unrelated parents. With the same partner the mother had had two previous pregnancies. The first resulted in a healthy term female infant weighing 3900 g, who at 4 years continues to be well. The second pregnancy

Phenotypic features of index case, a previously reported case, duplication 3p, and deletion 9p

Clinical features	Previous case ¹	Index case	Duplication 3p	Deletion 9p
Head and neck				
Flat occiput	+	-	-	+
Narrow bifrontal diameter	+	-	-	-
High forehead	+	+	+	+
Frontal bossing	+	-	+	+/-
Full cheeks	+	+	+	-
Micrognathia	+	-	+	+
Short, broad neck	+	-	+	+
Capillary haemangiomas (forehead, occiput, neck)	+	-	-	-
Eyes				
Hypertelorism	+	+	+	+
Prominent	+	-	-	-
Almond shaped	+	-	-	-
Upward slanting	+	-	-	+
Bilateral epicanthic folds	+	+	+	+
Ears				
Horizontal earlobe crease	-	+	+	+
Overfolded	+	-	+	+
Anteflexed, anteverted	+	-	+	+
Posteriorly angulated	+	-	-	-
Nose				
Small	+	-	+	-
Wide and flat nasal bridge	+	+	+	+
Anteverted nares	+	-	-	+
Mouth				
Long philtrum	-	+	-	+
Small	+	-	-	+
Overhanging upper lip	+	-	+	-
Downturned corners	+	+	+	-
Trunk				
Widely spaced nipples	+	-	+	+
Obesity of trunk & thighs	+	+	-	+
Hypotonia	+	+	+	+/-
Hypoplastic clitoris & labia minora	+	-	+/-	+/-
Limbs				
Long thumbs	+	-	-	+
Arms anteriorly displaced	+	-	-	-

Figure 1 Front view of face illustrating hypertelorism, wide, flat nasal bridge, high forehead, and long philtrum. Note the presence of a nasogastric feeding tube.

ended in a spontaneous abortion of unknown cause at 14 weeks' gestation. There was no known significant family history.

The proband was born at 40 weeks' gestation after an uncomplicated pregnancy. Apgar scores at birth were 9 and 9 at one and five minutes respectively. Birth weight was 4210 g (greater than the 90th centile for gestation), length 55 cm (greater than the 97th centile), and head circumference 36 cm (90th centile).

On examination (fig 1) at birth she was noted to be macrosomic with increased body hair, particularly on both ears. She also had marked generalised hypotonia, but there was no organomegaly, exomphalos, or macroglossia noted. Minor anomalies noted were mild hypertelorism, a saddle shaped bridge of the nose, a relatively long philtrum, a small, down turned mouth, and a shallow, single, horizontal crease on both pinnae.

Shortly after birth, she developed signs of profound hypoglycaemia which was confirmed by serum glucose measurement. She required intravenous dextrose for 13 days before a normal blood glucose could be maintained by oral feeding only. The exact aetiology of the hypoglycaemia was not elucidated.

Initially, milk feeds had to be given through a nasogastric tube. It took until 12 weeks of age before full bottle feeds could be established.

Aged 11 weeks she had had no recurrence of hypoglycaemic symptoms, although she was still profoundly hypotonic. She had reasonable

visual awareness, but smiled rarely. Her hearing appeared intact. Her growth parameters were all well above the 97th centile. All investigations, including extensive radiographic and biochemical tests, have been normal to date.

High resolution banded (GTL) chromosomes were obtained from peripheral blood lymphocyte cultures shortly after birth and showed the proband to have an abnormal 9p+ chromosome. The father was found to have an apparently normal male karyotype, but the mother carried the balanced reciprocal translocation 46,XX,t(3;9)(p25;p23). The karyotype of the proband was therefore 46,XX,-9,+der(9)t(3;9)(p25;p23)mat (fig 2).

Generally the present case has mild phenotypic features, some of which are shared with both dup(3p)³ and del(9p)^{5,6} syndromes, such as a high forehead, short neck, hypertelorism, epicanthic folds, dysmorphic ears, and a flat nasal bridge (table). Features shared with the dup(3p) syndrome alone include full cheeks, a small nose, and the appearance of the mouth. Marked hypotonia is found in the dup(3p) syndrome while both hypotonia and hypertonia have been reported in del(9p) syndrome.⁵ A long philtrum and obesity are features shared with del(9p) syndrome. Indeed, a birth weight greater than the 90th centile was also seen in the previous case with this chromosome abnormality.¹ The repeated reports of macro-

Figure 2 G banded partial karyotypes of chromosomes 3 and 9 for (A) the mother and (B) the proband. Arrows on the chromosomes and ideograms indicate the translocation breakpoints.

somia in patients with a deleted 9p may suggest an overgrowth syndrome.¹

The appearance of the proband was quite similar to the previous case reported (table) as was the prolonged hypoglycaemia and hypotonia. The hairy ears of our patient have not been previously reported in related cases.

These findings confirm those of the previous report and represent an unusually mild phenotype for the degree of chromosome imbalance. The abnormal chromosome 9 has been inherited from the same parent in each case and an advantageous genomic imprinting effect from maternal meiosis is a possibility for the duplicated segment of 3p. Imprinting appears not to have a role in this region of 9p.⁶ It can also be inferred from this case that this portion of chromosome 9 is important in glucose re-

gulation. The phenotype may be complicated in males by sex reversal² which is a feature of the deletion of chromosome 9p.⁷

- 1 Game K, Friedman JM, Kalousek DK. Mild phenotypic abnormalities in combined del9p2 and dup3p2. *Am J Med Genet* 1990;35:370-2.
- 2 Fryns JP, Kleczkowska A, Casaer P, Van Den Berghe H. Double autosomal chromosomal aberration (3p trisomy/9p monosomy) and sex reversal. *Ann Genet (Paris)* 1986; 29:49-52.
- 3 Conte RA, Pitter JH, Verma RS. Molecular characterization of trisomic segment 3p24.1→3pter: a case with review of the literature. *Clin Genet* 1995;48:49-53.
- 4 Young RS, Reed T, Hodes ME, Palmer CG. The dermatoglyphic and clinical features of the 9p trisomy and 9p partial deletion syndromes. *Hum Genet* 1982;62:31-9.
- 5 Huret JL, Leonard C, Forestier B, Rethoré MD, Lejeune J. Eleven new cases of del(9p) and features from 80 cases. *J Med Genet* 1988;25:741-9.
- 6 Micalé MA, Haren JM, Conroy JM, Crowe CA, Schwartz S. Parental origin of de novo chromosome 9 deletions in del(9p) syndrome. *Am J Med Genet* 1995;57:79-81.
- 7 Bennett CP, Docherty Z, Robb SA, Ramani P, Hawkins JR, Grant D. Deletion 9p and sex reversal. *J Med Genet* 1993; 30:518-20.