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A. J. H. HAMERS AND CA. VAN KEMPEN

Huize 'Maria Roepaen',
Institute for Mental Defectives,
Ottersum, The Netherlands

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Requests for reprints to Dr A. J. H. Hamers, Huize 'Maria Roepaen', Institute for Mental Defectives, Siebengewaldseweg 15, Ottersum, The Netherlands.

An interstitial deletion of chromosome 9 in a girl with multiple congenital anomalies¹

SUMMARY An infant with peculiar facies, coloboma of both eyes, and developmental retardation was found to have a *de novo* interstitial deletion of the secondary constriction and some adjacent euchromatin on one of her No. 9 chromosomes, del(9)(q11q21). Since studies on duplications, variants, and the molecular composition of the secondary constriction suggest that it contributes little if any information necessary to normal development, deletion of the euchromatin alone is most probably responsible for the clinical findings.

An extensive literature now exists on the various trisomies of chromosome 9 and their clinical significance (Sutherland *et al.*, 1976). In contrast relatively few data are available regarding deletions of this chromosome. Alfi *et al.* (1976) have studied 6 patients with deletions of the short arm distal to 9p22 and have found consistency in the resulting clinical malformations. Smith *et al.* (1973) reported a unique long arm deletion with associated persistent fragments in a severely malformed boy. In this case, specific identification of the deleted material was difficult. An institutionalised male with a 46,XY,9q- karyotype was reported by Newton *et al.* (1973). The deleted segment in this patient was identified as the secondary constriction. Ring chromosomes resulting from elimination of small amounts of distal chromosomal material have been reported by Jacobsen *et al.* (1973) and Kistenmacher *et al.* (1975).

We wish to report our observations on a child with a new deletion, one which resulted in loss of the secondary constriction and a small amount of adjacent euchromatin. The patient presented with developmental retardation and multiple congenital anomalies.

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Case report

The patient was born to a 22-year-old father and a gravida I para I 21-year-old mother. There was no indication of consanguinity, and the family history was unremarkable. The pregnancy was complicated by mild toxæmia, but no medication was taken. Delivery, in which the mother suffered a mild convulsion, was premature at 32 weeks' gestation. The patient's birthweight was 1842 g (4 lb 1 oz), length 42 cm, and head circumference 30 cm. Apgar scores of 6 at 1 minute and 8 at 5 minutes were given. The infant was jaundiced, with the highest bilirubin level, 12, occurring at 3 days. She was treated under the bilirubin reduction light and discharged at 6 weeks with a weight of (2435 g) 5 lb 6 oz. A peculiar high pitched cry was noted in the nursery.

An accidental fracture of both tibia and fibula was reported at 3 months. At 5 months, the baby's cry was no longer remarkable. She was alert and active, holding objects in both hands, taking objects to her mouth, and rolling over. No feeding problems were encountered. Physical examination disclosed brachycephalism with frontal bossing. The anterior fontanelle was open, normal in size, and extending to the metopic suture. Tension was not raised. The posterior fontanelle was closed. Her length was 55.9 cm, weight 4082 g (9 lb), and head circumference 35.6 cm. Hypertelorism, strabismus, and low set ears with prominent pinnae were noted. The palate was normal. Ophthalmic examination disclosed choroidal colobomas in both eyes, the right involving the optic nerve. The prognosis for useful vision was poor, but central vision was judged probable for the left eye. A small umbilical hernia was present, but heart, lungs, central nervous system, genitalia, joints, and skin were all normal. No signs of skeletal abnormalities were found.

The child was examined again at 15 months, and no changes in her physical appearance were noted. Her length, 72.4 cm, and head circumference, 44.4 cm, were just above the 3rd centile. Her weight, 8131 g (17 lb 15 oz), was in the 3rd centile. She sat alone at 10 months and spoke at 1 year. Her first teeth emerged at 1 year. At 16 months she was evaluated on the Cattell Infant Intelligence Scale and given a mental age of 8.8 months. At 16.5 months (Fig. 1) the patient was active and walking with support.

Analysis of dermatoglyphs revealed certain variations from the normal. Total finger ridge count was 66, well below the average for a Caucasian female (Alter, 1969). On the palms, no patterns were seen in the hypothenar, thenar/1st interdigital, 2nd or 3rd interdigital areas. A loop was observed in the left 4th interdigital area. The *atd* angle was raised on both palms.

Fig. 1. *The proposita*, age 17 months.

The results of CBC, urine, and amino acid evaluations were all within normal limits. An SMA-12 evaluation obtained at 15 months gave the following significant paediatric values: alkaline phosphatase 183 (30–160), creatine kinase 230 (25–145), and lactate dehydrogenase 330 (90–200). Serum and red cell markers obtained from the patient and her parents were evaluated at the Galton Laboratory, University College, London, and the Michigan State University Department of Medicine Laboratory at the Mid-Michigan Regional Red Cross Blood Center. No abnormalities were detected. These results appear in the Table.

Chromosome studies

Chromosome studies were initiated at age 5 months. Slides prepared from short term peripheral blood culture and regular Giemsa staining showed a 46,XX complement with one C group chromosome replaced by a small metacentric chromosome slightly larger than a No. 16. No indication of mosaicism was found. Giemsa banding confirmed that the chromosome in question was a No. 9. Neither C nor Q banding gave any indication of a secondary constriction. C banding revealed a small amount of darkly staining material at the centromere; this we interpreted as centromeric heterochromatin. Reverse Giemsa banding was used to show the nature of the deletion (Fig. 2 and 3). The appearance of the reverse banded deleted 9 is compatible with loss of the secondary constriction and some adjacent euchromatin. R banding shows telomeric staining on the long arm, and a small amount of lightly stained material proximal to the darkly stained band 9q22.

Table Summary of phenotypes of genetics markers

	ABO	D	C	c	E	e	M	N	S	s	P	Le ^a	Le ^b	K	Fy ^a	Fy ^b	Jk ^a	Hp	Tf	PGD	PGM	Ak	ADA	GPT	Pl	Gc	Gm	Ino	ES-D	SGOT
Proposita	A ₂	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1-1	C	A	1	1	1	1	M	1	-	1+	1	1
Father	O	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2-1	C	A	1	1	1	1	M	1	-	-	1	1
Mother	A ₂	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1-1	C	A	1	1	1	1	M	1	-	-2	1	1

Fig. 2 R band karyotype of the probanda showing *del(9)(q11q21)*.

Fig. 3 Partial karyotype from the probanda. Normal 9 is on the left, *del(9)(q11q21)* on the right. From left to right: G bands, R bands, Q bands, and C bands.

This corresponds to a portion of 9q21, which stains darkly with G banding procedures. The slightly enlarged band near the centromere seen on the G banded deleted 9 in Fig 3 is consistent with an assignment of the distal break point to 9q21. Evaluation of all banding results places the proximal break point in 9q11. The telomeric bands seen on the R banded chromosomes are not consistent with inversion of the remaining segment of the long arm. The description of this deletion is 46,XX,*del(9)(q11q21)*. Both parents were found to have normal karyotypes, and both had noticeable secondary constrictions. C banding of both parents failed to disclose the origin of the deleted chromosome. There is no evidence for translocation in any of the individuals karyotyped.

Discussion

To our knowledge, this is the first report of an interstitial deletion of the secondary constriction and euchromatin closely adjacent to it on chromosome 9. Because of her initial cat-like cry and other suggestive features, the patient was originally diagnosed as having the 5p- syndrome. A combination of banding techniques was required before the chromosomal

abnormality was fully characterised. The patient's present clinical manifestations include developmental retardation, peculiar facies, and defective vision. Some component of her developmental retardation and the strabismus may be secondary to loss of sight in the right eye and its limitation in the left. Mental retardation of the mild form is probable, but the patient's age and visual handicap preclude an adequate diagnosis at this time. The child is otherwise active and alert, and her other systems appear normal.

The deletion has resulted in the loss of both heterochromatin and euchromatin. No significant relation between the secondary constriction and normal development is yet established. An array of functions for regions rich in satellite DNA has been proposed (Yunis, 1974, for review) with regulatory and structural roles favoured over transcriptional or translational ones. Variants of the secondary constriction include apparent duplications and deletions of the heterochromatin and have not been associated with any clinically definable anomalies. The accumulated data so far suggest that informational DNA essential to normal development may be lacking in this area of chromosome 9. In our case, the clinical findings are presumably the result of a deficiency of bordering

euchromatin in bands 9q11, 13, and 21. This hypothesis finds support in cases of trisomy 9p where additional long arm material was also present. These cases have recently been reviewed by Sutherland *et al.* (1976). Though mild urogenital abnormalities were present in addition to 9p+ symptoms in some patients trisomic for 9pter→9q11 or 12, the accumulation of additional malformations was striking in those individuals trisomic for additional material distal to 9q13. Micrognathia, urogenital anomalies, cranial suture abnormalities, and early death were noted in patients trisomic for 9pter→9q2. It is possible that the most significant lesion in our case was loss of part of band 9q21.

Deletion mapping studies indicated no segregational abnormalities for the red cell or serum markers tested. Since both parents had normal karyotypes, the rearrangement originated *de novo*, probably in gametogenesis. C banding was performed on both parents in the hope of determining the origin of the rearrangement via No. 9 secondary constriction polymorphisms. The secondary constrictions of both parents were normal in size and uninformative. A normal male child has since been born to the couple.

The multiple anomalies of our patient do not fall into the pattern of any recognised chromosomal syndrome. With the exception of ring chromosomes, only two other cases of long arm deletion have been reported. The patient of Smith *et al.* (1973) had unusual facies, lumbosacral myelomeningocele, dilatation of the ventricles, upward slanting of the palpebral fissures, a heart murmur, bilateral talipes equinovarus, partial malrotation of the bowel, and urogenital abnormalities. A very confusing cytological picture emerged for this patient, a deletion of two-thirds of the long arm and the presence of one or two presumably related fragments. An exact description of the deleted material was not reported. The second case, that of Newton *et al.* (1972), was found to have a 9q- chromosome similar in appearance to a No. 16, as in our patient. Here, fluorescent staining revealed a *de novo* deletion of the secondary constriction; no loss of adjacent euchromatin was reported. Clinically, a comparison of these two patients does not suggest a syndrome. The case of Newton *et al.* (1972), a 22-year-old institutionalised man, was found to have epilepsy, hypertelorism, contracture of the left elbow, hyperextensibility of the metacarpophalangeal joints, and an IQ judged to be untestable. The only points of similarity with our case are hypertelorism and, possibly, mental retardation.

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LAWRENCE WISNIEWSKI¹, GERALD PURDY¹,
TERRY HASSOLD¹, CAROLA WILSON¹, KAREN
BENTLEY², EMANUEL HACKEL^{1,3}, AND JAMES
V. HIGGINS^{1,4}

¹Department of Zoology, Michigan State University, East Lansing, Michigan, U.S.A.

²Department of Pediatrics, Hurley Hospital, Flint, Michigan, U.S.A.

³Department of Medicine Michigan State University, East Lansing, Michigan, U.S.A.

⁴Department of Human Development, Michigan State University, East Lansing, Michigan, U.S.A.

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Requests for reprints to Dr Lawrence Wisniewski, Department of Human Development, B 240 Life Sciences I, Michigan State University, East Lansing, Michigan 48824, U.S.A.

Partial trisomy 20 (20q13) and partial trisomy 21 (21pter→21q21.3)¹

SUMMARY A patient with a double partial trisomy 20 and 21 with mild mental retardation and multiple congenital anomalies is presented. Despite trisomy for a substantial portion of chromosome 21, the patient showed only minor stigmata compatible with Down syndrome.

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