FIGURE Two different origins of an XX/XY (a) through lagging and (b) through non-disjunction.

identity of all markers if the child is a chimera and not a mosaic.

EARLY EMBRYOLOGY AND MOSAICISM

Before drawing a final conclusion we examined the plausibility of a mosaic origin in the early embryo. The two most economical hypotheses are shown in the figure.

An XXY zygote is postulated. Clearly, both XX and XY cell lines could not originate before the second cleavage division. Other hypotheses involving lagging or non-disjunction or both at later divisions of the embryo are also possible, but none would yield a cell population in which more than 50% of the cells were of the two types, XX and XY, unless, of course, differential proliferation of cells with different karyotypes occurred. We prefer to avoid such an assumption although it would favour our case.

Current views on the early embryology of both mouse and man are that only three or four cells in a mammalian blastocyst are selected as progenitors of the embryo proper.¹⁰ Thus it seems likely that precocious non-disjunctional events could produce karyotypically distinct lines present in the placenta or in the fetus but not necessarily in both. Demon-

stration of this can be seen in the papers of Kalousek and Dill¹¹ and Simoni *et al.*¹² who found examples in man of chromosomal abnormalities confined to extraembryonic tissues. On the basis of the analyses of chromosomal polymorphisms and genetic markers, we therefore conclude that our XX/XY case is a mosaic rather than a chimera.

During the preparation of this paper C E Ford was visiting Professor at the University of Pavia. The authors are grateful to Dr Patricia Tippet for determining the blood groups and to Professor M Fraccaro for stimulating discussion.

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Clinical manifestations of trisomy 5q

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SUMMARY A patient with a small deletion of the short arm and a partial duplication of the

long arm of chromosome 5 is described. The main clinical features include craniofacial dysmorphism, growth failure, developmental retardation, and congenital heart defect. The

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(a)

(b)

FIG 1 (a) Lateral view of the face showing well formed, low set ears, small receding chin, and low posterior hair line with short neck. (b) Front view of the face. Dysmorphic features to note are prominent and wide nasal bridge, small palpebral fissures with downward slant, small nose with wide nasal alae, long philtrum, thin upper lip, carp mouth, microstomia, and small chin.

mother and male sib each carried an inv(5) (p15.3q35) but were phenotypically normal. The possible clinical manifestations of partial duplication of the long arm of chromosome 5 are discussed with a review of previous published reports.

The phenotypic similarities in patients with apparently identical structural anomalies are important in establishing karyotype-phenotype correlations for particular trisomies and monosomies. The clinical manifestations of partial 5q duplication have been reported involving different chromosomal segments. Three specific subgroups are provisionally recognised.¹ In the present report we describe the clinical features of a case with a duplication of the negative

band 5q35→qter and compare it with previously reported cases with similar and different duplicated segments of the long arm of chromosome 5.

Case report

Our patient was born on 30.5.82 to unrelated Caucasian parents. It was the second pregnancy of a 25 year old mother who had no significant medical history. The pregnancy was uneventful and the delivery was normal, vertex, and at term. Birth weight was below the 3rd centile (2268 g) and Apgar score was 10 at one minute. She was noticed to have a small head (circumference 29.7 cm, below the 3rd centile). The crown to heel length was 39.5 cm (below the 3rd centile). The anterior fontanelle was noted to be very small, possibly due to cranial synostosis. The

TABLE Clinical and cytogenetic findings in partial duplication of the long arm of chromosome 5 in the present case and the previously reported 18 cases, arranged according to the segment involved from proximal to distal.

	Jalbert et al ¹	Gilgen- krantz et al ⁵ Case 1	Case 2	Martin et al ⁷	Ferguson- Smith et al ⁸	Osztovcics and Kiss ⁹ Case 1	Case 2	Jones et al ¹⁰
Duplicated segment	5q11→q22	5q13→q22		5q22→q33	5q31→qter	5q31→qter	5q31→qter	5q31→qter
Age (at examination)	3y 7mth	4y		4mth	4y	8mth	10mth	2mth
Sex	F	F	F	M	M	F	F	F
Maternal age	24	22	26	20	26	24	29	23
Gestation (wk)	40	—	—	38	—	39	38	36
Birth weight (g)	2880	2300	700	2290	—	2650	2700	2190
Birth length (cm)	—	46	31	47.5	—	42	49	43
Head circumference (cm)	—	—	—	30.5	—	—	—	30
Growth/mental retardation	±	+	—	+	+	+	+	+
Craniofacial dysmorphism	+	+	+	+	+	+	+	+
Microcephaly	—	—	—	+	+	+	+	+
Short, receding forehead	—	—	—	—	—	—	—	—
Antimongoloid slant	—	+	+	—	+	—	—	—
Epicanthus	—	—	—	—	—	—	+	—
Strabismus	+	—	—	—	—	+	+	—
Hypertelorism	—	—	—	—	+	+	—	—
Prominent nasal bridge	+	+	+	—	—	—	—	+
Upper lip: large/thin	—/+	—/+	—/+	+/+	—/=	+/.	—/.	+/.
Low set/dysplastic ears	+	+	—	+	+	+	+	—
Philtrum: long/short	—	—	—	—	—	—	—	—/+
Carp mouth/microstomia	—	—/+	—/+	—	—	—	—/—	+/+
Muscle hypotrophy	+	+	—	—	—	—	—	—
Hypotonia	+	—	—	—	—	—	—	—
Brachydactyly/clinodactyly	—/—	—	—	+/+	+/+	+/—	—/—	+/—
Hernias	—	—	—	—	—	+	—	—
Congenital heart defect	+	—	—	+	—	—	+	+

+ = present, — = absent, (.) = no data.

FIG 2 Microphotograph of the banded chromosome 5 showing inv(5)(p15.3;q35) as seen in the mother and brother, and partial duplication of the long arm of chromosome 5 in the proband.

ears were low set and the upper half of the face was poorly developed, but the palate was intact. Cardiac auscultation at four weeks of age revealed an ejection systolic murmur which was thought to be due to a ventricular septal defect. There were significant feeding problems and she was followed up for failure

to thrive and developmental delay. Subsequent progress was complicated by afebrile seizures which were controlled by sodium valproate (Epilim). There was no family history of mental retardation or birth defect. Her four year old brother is phenotypically normal.

Physical examination at the age of 14 months revealed an active healthy girl with dysmorphic features. The crown to heel length was 62.5 cm (below the 3rd centile) and the head circumference was 39 cm (below the 3rd centile). The shape of the head was brachycephalic and the metopic suture was prominent. All the sutures were fused and no fontanelle was palpable. The posterior hair line was low with a short neck. The eyes were prominent with small oblique palpebral fissures with a downward and outward slant. The outer canthal distance was 6 cm (25th centile). Inner canthal distance (2 cm) and interpupillary distance (4 cm) were both around the 50th centile. The nose was small with wide nasal alae and a prominent bridge. The ears were well formed but low set (fig 1a). The mouth was small with thin lips and a small receding chin (fig 1b). The palate was high arched but intact. The alveolar margins were normal with only two lower incisors erupted. Hands and feet were small but normal. The spine was normal apart from mild scoliosis. The external genitalia were normal female. Cardiovascular examination revealed a 2/6 ejection systolic murmur at the

<i>Rodewald et al^l Case 1</i>	<i>Case 2</i>	<i>Bartsch- Sandhoff and Liersch¹ Case 1</i>	<i>Case 2</i>	<i>Zabel et al¹²</i>	<i>Passarge et al^b</i>	<i>Curry et al³ Case 1</i>	<i>Case 2</i>	<i>Case 3</i>	<i>Case 4</i>	<i>Present case</i>
5q31→qter 3y 2mth	6 mth	5q31→qter 4mth	7y	5q33→qter 2mth	5q33→qter 4mth	5q34→qter 22y	21y	21y	16y	5q35→qter 16mth
F	F	F	F	M	M	F	F	M	M	F
25	30	28	22	33	—	28	29	19	25	25
38	40	38	—	40	38	—	—	—	—	40
1700	2700	2400	3250	2460	—	2940	2760	2760	2724	2200
37	47	47	51	46	—	—	—	—	—	39.5
32	32	32	37	33.2	—	—	—	—	—	29.7
+	+	+	+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+
+	—	—	—	—	—	+	+	+	+	—
+	—	—	+	+	+	.	.	.	.	+
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+	+	+	—	+	+	—	—	+	+	+
—	.	.	.	.	+/-	+/-	+/-	+/-	+/-	-/+
+/+	+/+	+/+	+/+	-/+	—	—	—	—	—	+/+
+	.	.	.	—	—	—	—	—	—	—
+	.	.	.	.	—	.	.	.	.	+
+	+/+	—	—	-/-	.	+/+	+/-	—	—	+/-
+	.	+	+	+	+	—	—	+	+	—
+	.	+	+	.	+	.	.	+	+	+

apex, audible along the left sternal edge. Examination of the central nervous system was normal, except for a mild degree of muscular hypotonia. Developmentally, she was functioning at around 10 months of age. Vision and hearing were both normal. Speech was limited to monosyllables (ma, pa). Socially, she showed interest in strangers and made attempts to respond to commands.

Dermatoglyphic examination revealed normal axial triradii and complex palmar creases. There were three whorls, three arches, and one radial and two ulnar loops on the fingertips and the *atd* angle approximated 45°. X ray of the skull was normal and CT scan did not show any intracranial malformation. X ray of the chest indicated left ventricular hypertrophy and increased pulmonary vasculature. An echocardiogram showed an atrial septal defect of secundum origin. There was no evidence of a ventricular septal defect. ECG showed ectopic beats, probably of ventricular or junctional origin. The nature of the underlying cardiac lesion was thought to be cardiomyopathy. The patient has been reported to be progressing satisfactorily.

CYTOGENETIC FINDINGS

The patient was referred for cytogenetic evaluation at 14 months owing to a general failure to thrive. Lymphocyte preparations were made according to

the routine methotrexate method used in this laboratory.² Chromosome 5 showed a small additional negative staining fraction of material at the end of the short arm (fig 2). In order to discover the origins of this material, the parents, maternal grandparents, and an elder sib were also referred for cytogenetic analysis. Thus it was found that both the mother and sib carried an inverted chromosome 5 (p15-3q35) with the terminal negative band of the long arm being relocated at the end of the short arm (fig 2). It can, therefore, be assumed that the abnormal chromosome in the proband arose as a result of meiotic recombination, giving a product which carries the terminal negative band of the chromosome 5 long arm at both ends of the chromosome, and is missing a small piece of the chromosome 5 short arm. This product is described as rec(5),dup q,inv(5)(p15-3q35)mat. The case represents a manifestation of a small chromosomal rearrangement detected by the methotrexate banding technique.

Discussion

Curry *et al*³ described four patients from the same family with an identical chromosome abnormality (duplication and deletion), involving partial trisomy of chromosome 5 (dup(5)(q34→qter). They attributed the clinical features noted to the duplication present

and provisionally identified a distinctive clinical syndrome. This interpretation was accepted by Rodewald *et al*¹ who further suggested that three clinically distinguishable phenotypes could be identified according to the particular region of the long arm of chromosome 5 duplicated. The first syndrome, corresponding to the proximal duplication 5q11→q22, and then described in only a single case,⁴ was not supported by the report of Gilgenkrantz *et al*.⁵ The other syndromes correspond to duplications of 5q31 or 5q33→qter and that of 5q34→qter. These latter syndromes shared most clinical features which were considered to be less severe in those patients with the smaller duplications.³

Passarge *et al*⁶ described three cases with duplication/deficiency and identified a distinct phenotype. They expressed the opinion that this phenotype was the result of duplication 5q33→qter rather than the chromosomal deficiency (8q23→qter) also present. These authors drew attention to the similar phenotype observed in two previous patients with duplication of 5q31→qter. Martin *et al*⁷ described a patient with pure duplication of 5q22→q33 and noted the similarity of phenotypic findings to previously described patients with partial trisomy for the long arm of chromosome 5.

The most common features of the reported patients (table 4) with partial trisomy 5q, almost all involving at least q35→qter, are growth and mental retardation, microcephaly, craniofacial dysmorphism including antimongoloid slant, strabismus, prominent nasal bridge, and low set dysplastic ears, brachydactyly or clinodactyly or both, and heart defect. Our case (dup 5q35→qter) has all these apart from strabismus. It is not possible to state that the dysmorphism in our patient is less severe than in the patients with larger duplications of chromosome 5. We are doubtful that this combination of features constitutes a specific clinical syndrome, for each is a common manifestation of chromosome abnormality and the total pattern is not sufficiently distinctive. There seems to be no real justification, on present evidence, for recognising clinical subgroups corresponding to the particular region of the long arm of chromosome 5 duplicated. Previous authors have rightly drawn attention to the difficulty of interpreting the significance of phenotype/chromosome

abnormality correlations where mixed chromosome abnormality is observed, especially when that mixture is different in different families or patients. Nevertheless, further observations on new cases may delineate a specific phenotype correlation, at least with the length of the chromosomal segment involved.

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