particular mosaics have an increased risk of abnormal offspring.⁶ It has also been suggested that the increased risk of single organ malformations in the progeny of Turner and triple X women may be related to their premature ovarian ageing.⁷ In the present case, the mother had two or three miscarriages during her fertile years and following the birth of the proband she suffered premature menopause.

Gonadal dysgenesis is a constant feature of all X fusion chromosomes regardless of whether they are attached by the long or the short arms, or whether there is a 45,X cell line present. In the present case it is impossible to be certain whether she had truly completed pubertal development and had a menarche, or whether the menstrual losses and secondary sex characteristics had been entirely produced by exogenous hormones. However, by the time of investigation the girl had ovarian failure associated with dysgenetic ovaries. If, as indicated by the normal stature, there had been no loss of genetic material, this finding would confirm the belief that gonadal malfunction in Xp fusions cannot be explained solely on the basis of Xp deletion.⁸ This had previously been inferred from the finding that females with a deletion of the terminal portion of Xp are fertile.^{9,10} There was a 45,X cell line in the lymphocytes and fibroblasts from gonadal tissue in this patient which could have influenced the development of the gonads, but in other cases of Xp fusions without evidence of mosaicism gonadal malfunction still occurs. It is possible that the actual size of the abnormal chromosome leads to problems in pairing at meiosis, so that the primary oocytes which rest in the first prophase of meiotic division until puberty are unstable and consequently become atretic. This would be a similar situation to that of

the male where regular pairing of the X and Y chromosomes as a bivalent is a prerequisite for normal sperm formation.¹¹

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Translocation X;13 in a patient with retinoblastoma

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SUMMARY We describe the clinical and cytogenetic findings in a child with retinoblastoma and a translocation between chromosomes X and 13. The X;13 translocation in this patient does not involve band 13q14, the assigned locus for retinoblastoma.

Retinoblastoma (Rb) is a childhood retinal cancer with an incidence of 1 in 20 000 births¹ that occurs as a sporadic or a hereditary disease, the latter being a highly penetrant (95%) autosomal dominant trait. About 5% of retinoblastoma patients have a chromosome aberration.² This is usually an interstitial deletion of the region 13q14, but balanced translocations³ with breakpoints in this region have been reported, and the locus for Rb has been

assigned to 13q14.11.⁴ Two female patients with bilateral retinoblastoma and an apparently identical (X;13) balanced translocation have been reported.^{5,6} In both, the breakpoint on chromosome 13 was not at 13q14 but at 13q12, while the breakpoint on the X chromosome was at p22.

We report here a third case of bilateral Rb in a patient with a translocation between chromosomes X and 13 with different breakpoints, 46,X,t(X;13)(q12;q31).

Case report

The female infant was born on 29.12.80 after an uneventful 42 week pregnancy and weighed 2159 g (3rd centile). The father and mother were healthy and unrelated and aged 29 and 27 at the time of birth. At birth the infant showed hypertelorism, strabismus, epicanthus, short philtrum, dolichocephaly, diastatic cranial sutures, facial asymmetry, and loose ligaments, and congenital bilateral opacity of the crystalline was observed soon afterwards (fig 1). There was no reaction to sound, light, or environmental stimuli. Later on, there was a history of poor feeding, repeated infection, and irregular sleeping-waking pattern.

No signs of rubella, cytomegalovirus, or herpes simplex infections were found. T3 and T4 levels, urinary mucopolysaccharides, lysosomal enzymes, immunoglobulins, serum amino acids, and proteins were in the normal range.

An ultrasound examination of both eyes at 10 months suggested the presence of bilateral retino-

blastoma. This was confirmed by a CT scan. At follow up, the child showed generalised hypotonia, failure to thrive, severe psychomotor delay, and several episodes of pneumonia. She died at 18 months. Necropsy showed severe hydrocephalus, bilateral retinoblastoma without invasion of the optic nerve, bilateral bronchopneumonia, and hepatic and renal congestion. No metastases were found in any of the organs examined.

Materials, methods, and results

Chromosomes cultured from peripheral blood after GTG and RBA banding showed a balanced translocation involving chromosomes X and 13, 46,X,t(X;13)(q12;q31) (fig 2). The replication pattern of the X chromosomes studied in lymphocytes (50 mitoses) and in fibroblasts (28 mitoses) showed that the normal X was consistently late replicating. The parents had normal chromosomes. Q band studies from the proband and her parents did not reveal the origin of the translocation.

Esterase D (ESD) was assayed in erythrocytes and cultured fibroblasts by the method of Sparkes *al.*⁷ The levels of activity of ESD in erythrocytes and fibroblasts from the proband are compared with controls in the table. In the proband's erythrocytes the levels of ESD activity were higher than the mean for the controls, while in fibroblasts they were similar to those of controls. Arylsulphatase A (ARSA), tested as a control enzyme, was assayed according to Galjaard.⁸

FIG 1 The patient at nine months of age.

TABLE Levels of ESD activity in erythrocytes and fibroblasts and of ARSA (the control enzyme) in the proband and a group of controls. All activities expressed as nmol/mg/h.

	ESD	ARSA
Erythrocytes		
Patient	84.5	—
Controls (SD)	48.95 (14-80)	—
No	51	
Fibroblasts		
Patient	171.00	588.1
Controls (SD)	230.19 (129-24)	465.61 (211-69)
No	17	40

Discussion

The association between chromosome 13 abnormalities and retinoblastoma has been explained by assuming that the deletion caused by the effective or functional loss of an allele at the Rb locus is one of

the steps in the development of retinoblastoma. Cavanee *et al*⁹ have shown that tumour cells are homozygous for some restriction fragment polymorphism of chromosome 13 or ESD type for which the patients were heterozygous. This supports the hypothesis of Knudson¹⁰ that Rb results from the development of homozygosity for a mutant allele on chromosome 13. In the two X;13 translocations observed in patients with retinoblastoma,^{5,6} the breakpoint on chromosome 13 was far away from the Rb locus. In fibroblasts (but not in lymphocytes), this locus was, however, reached by the spreading of the inactivation from the X, resulting in a functional deletion.

In one case it was possible to demonstrate that inactivation also extended to ESD, thus confirming inactivation of the 13q14 region.⁶

The psychomotor retardation and growth impairment observed in these two patients could also be easily explained by the genetic imbalance present in cells with an inactivated der(X;13).

In our patient, the X;13 translocation did not involve band 13q14. Her tumour was apparently not the result of a functional deletion of genes on chromosome 13, since the normal X was late replicating in all lymphocytes and fibroblasts examined. Also, the normal levels of ESD activity were in agreement with the cytogenetic findings. However, the rarity of X;autosome translocations means that the Rb and the chromosome 13 abnormality are probably related.

We therefore postulate that a cell line with a late replicating der(X;13) chromosome, with spreading of inactivation over chromosome 13, was present in the very early stages of development and was then lost because of selective events against genetic imbalance.¹¹ The presence of such a line during brain and retinal development could explain the patient's severe mental retardation. At the same time, it would have caused a functional monosomy for the Rb allele.

In all cases of constitutive abnormalities of chromosome 13 leading to loss or inactivation of genes at band 13q14, a Rb mutation in the homologous chromosome 13 is needed to induce the development of Rb.⁴ Since in all reported cases of constitutive chromosome abnormality associated with Rb the latter appears to be sporadic, a high frequency of germinal or somatic mutation seems likely.

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Partial monosomy 12p13.1→13.3

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SUMMARY We describe a 27 month old female child with partial monosomy for the short arm of chromosome 12: 46,XX,del(12)(p13.1→p13.3). She differs from the eight cases described by others, in that she is less severely affected. Her main clinical features are developmental delay, protruding tongue, strabismus, slightly unusual facies, slight micrognathia, and speech delay.

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Case report

The child was born to 26 year old parents at term after an uneventful pregnancy. She has two normal siblings and her family history is unremarkable. Her birthweight was 3.62 kg, length 49.5 cm, and head circumference 34 cm. Early milestones were only slightly delayed. At 19 months she was referred for investigation of developmental delay, a squint, a protruding tongue (fig 1a), an unusual facies, and possible speech delay. Chromosome analysis was carried out as part of this investigation, her karyo-