

# A familial Xp+ chromosome, dup (Xq26.3→qter)

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**Abstract**

A maternally transmitted Xp+ chromosome was associated with an abnormal phenotype, including developmental delay and short stature, in two male cousins and their 12 year old aunt. The respective mothers were not mentally impaired but had short stature. The G banding pattern identified the extra chromosome segment as a repeat of Xq26.3→qter attached to an apparently intact Xp22.3 sub-band, so the Xp+ chromosome may be described as rea(X)(Xqter→p22.3::Xq26.3→Xqter). The rearranged chromosome was late replicating in 97 to 100% of the metaphases in the mothers but it was early replicating in 43% of the lymphocytes in the mentally defective female (n=100 cells/subject). Fluorescence in situ hybridisation using X and Y chromosome paints, as well as cosmids A and 1A1 specific for loci within Xq28, confirmed both the identity of the extra segment and the entirety of the Xp pseudoautosomal region. Therefore, the phenotypic consequences in this family can be related to the Xq26.3→qter functional disomy allowing for the effects of X inactivation in the female carriers.

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Partial Xq duplications usually involve bands proximal to q26 and are often ascertained through mentally retarded males in whom a distinct clinical picture has been associated with

Xq13.1→q21.1 disomy.<sup>1-3</sup> Four duplications extending into Xq27-28 have been described in phenotypically abnormal females,<sup>4</sup> but only a brother-sister pair<sup>5</sup> and a further girl<sup>6</sup> have had duplications limited to such distal bands. In the present context, only intrachromosomal Xq duplications are considered, that is, the numerous isochromosomes/isodicentric Xq and Xp;Xq translocations ascertained through female patients<sup>7</sup> as well as extra isochromosomes Xq in male patients<sup>8</sup> are disregarded. Here we report on a three generation pedigree in which a maternally transmitted Xp+ chromosome implying duplication Xq26.3→qter resulted in two boys and one girl with significant clinical abnormalities.

**Family report**

The proband (III·4, fig 1) was the first and only child born to a 25 year old 153 cm tall mother and a 26 year old father. He was delivered at term by caesarian section because of fetal distress; Apgar scores were 4 at one minute and 6 at five minutes. Birth weight was 2900 g. Thereafter, he had hypotonia, delayed milestones, failure to thrive, and respiratory infections requiring hospital management. At 5 months of age he had poor social contact and no head control. His length was 55 cm, weight 3850 g, and OFC 38 cm (all below the 3rd centile). He also had a tented upper lip, downturned corners of mouth, inguinal hernias, hypoplastic genitalia with undescended testes, and slender fingers and toes. There was neither ichthyosis nor radiological evidence of chondrodysplasia punctata. Family investigations disclosed two phenotypically abnormal relatives on the maternal side: a male cousin (III·3) and an aunt (II·6). The cousin was the third child of a 31 year old 152 cm tall mother and an unrelated 27 year old father; both sibs are healthy children. Delivery was at term and spontaneous but the infant required respiratory assistance because of severe asphyxia. Birth weight was 2500 g. His clinical manifestations at 7 months of age were very similar to those of the proband and included hypotonia, developmental delay, failure to thrive (length 58 cm, weight 4700 g, OFC 37·5 cm), fish shaped mouth, inguinal hernias, hypoplastic genitalia, and cryptorchidism. Ichthyosis and chondrodysplasia punctata were absent. He also had recurrent bronchopneumonia which resulted in death at 13 months of age. The 12 year old aunt had obvious short stature and mental retardation; microphthalmia and linear skin defects were not apparent but a detailed physical examination was denied. The maternal

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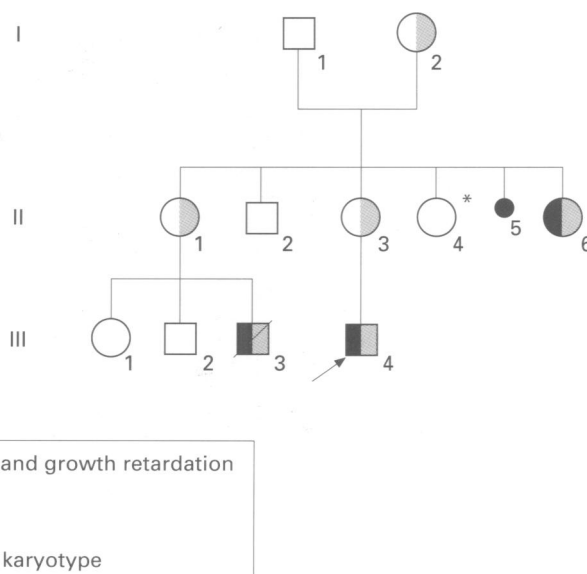


Figure 1 Pedigree.

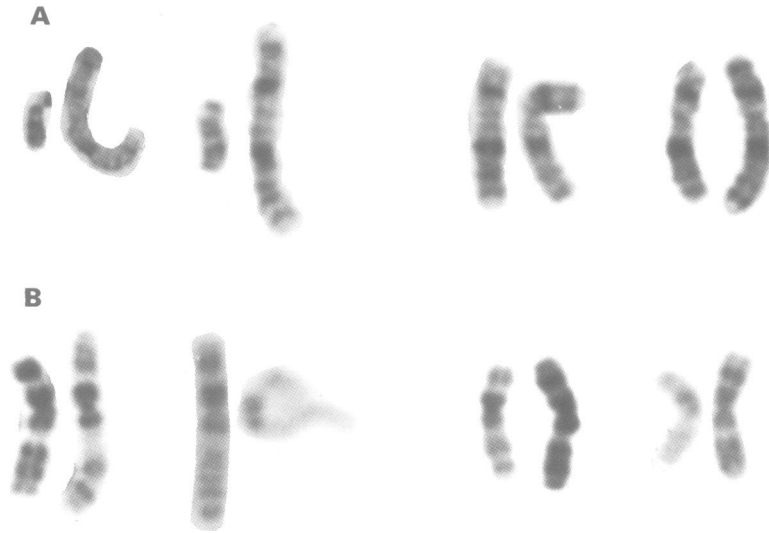


Figure 2 Sex chromosome pairs showing the Xp+ chromosome with duplication q26.3→qter (the Xp+ is on the right in each pair). (A) G bands. (B) Replication patterns in female subjects documenting the inactive (left hand pairs) or active (right hand pairs) status of the abnormal X chromosome.

grandmother was also short statured whereas the remaining maternal aunt (II·4) had a normal phenotype and a height of 167 cm.

#### CYTOGENETIC STUDIES

Chromosome preparations from standard whole blood cultures of the proband and several relatives were analysed after GTG banding.<sup>9</sup> Subsequently, X chromosome replication in the female carriers (see below) was assessed using a terminal 5-bromo-2'-deoxyuridine pulse followed by FPG staining.<sup>10</sup> Whole chromosome painting with X and Y specific libraries (Cambio, Cambridge) was done on metaphase spreads of the proband and subject II·1. The methodology was essentially that indicated by the manufacturer. The origin of the extra segment (see below) was further assessed in the proband by means of fluorescence in situ hybridisation<sup>11</sup> using the Xq28 cosmids A and 1A1 specific for the loci L1CAM and DXS305/374 respectively.

All three phenotypically abnormal subjects as well as their mothers were found to have an Xp+ chromosome within an otherwise normal (male or female) karyotype; in contrast, a 46, XX karyotype was found in subject II·4. The G banding pattern identified the extra segment as a repeat of Xq26.3→qter attached to an apparently entire Xp22.3 sub-band (fig 2). Therefore, the Xp+ chromosome may be described as a rea(X) (Xqter→Xp22.3::Xq26.3→qter). In all three mothers the Xp+ was predominantly inactive (97 to 100% of the metaphases) whereas in the mentally retarded girl it was either late (57%) or early (43%) replicating (n = 100 cells/subject) (fig 2). The X chromosome paint showed that the extra segment consisted only of X chromosome sequences whereas the hybridisation pattern of cosmids A and 1A1 confirmed the distal Xq duplication (fig 3). The Y chromosome paint showed an apparently normal pseudoautosomal region at p22.3 in the rearranged X

chromosome (fig 3). Cell lines are not available from any of these people.

#### Discussion

It is uncertain whether this abnormal chromosome resulted from a recombination within an untraced (either germinal or constitutional) pericentric inversion or from an inter-homologue translocation. Although telomeric sequences at the breakpoint junction were not looked for, neither their presence nor absence may unequivocally elucidate the origin as a pericentric inversion, which may result from a single break at Xq26.3 with transposition of the Xq distal segment onto the Xp telomere and healing of the broken end.<sup>12</sup> Regardless of the mechanism, the present Xp+ chromosome looks like an actual recombinant.<sup>5</sup>

The two male infants presented in this paper and one previously published boy with a similar imbalance<sup>5</sup> did not show ichthyosis or other exclusive stigmata of Xp22 nullisomy, a finding consistent with the very distal localisation of the Xp breakpoint in both rearrangements. Otherwise, males with duplications for other Xq segments also exhibit perinatal asphyxia, severe mental retardation, marked short stature, inguinal hernias, hypoplastic genitalia, and cryptorchidism.<sup>1-3,13</sup> Of particular relevance here are three severely affected boys with mental retardation, hypotonia, no speech development, seizures, short stature, and microcephaly secondary to disomy for 5–10 Mb of Xq28 resulting from aberrant Xq-Yq interchanges.<sup>14</sup> Remarkably, males with partial Xp duplications also show mental and growth retardation as major components of a phenotype that features sex reversion whenever the relevant gene is involved.<sup>15,16</sup> Taken together, the reported duplications cover the entire X chromosome with the exception of Xp11.1→q11 and confirm the assertion that partial constitutional disomies of this chromosome are compatible with postnatal survival

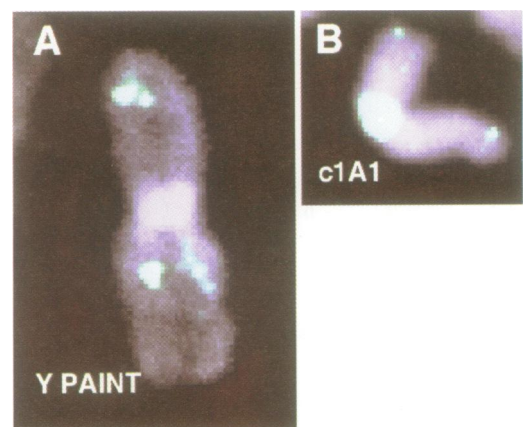


Figure 3 Image enhanced FISH results on the Xp+ observed in the proband. (A) Painting with a whole Y chromosome paint library gave complete coverage of the euchromatic region of the normal Y (not shown) and cross hybridisation to the interstitial pseudoautosomal region in distal Xp of the abnormal X and also to Xq21. (B) The cosmid 1A1 (DXS305/374), which maps to Xq28, showed signal both at Xq28 and at the distal tip of Xp.

of the affected males.<sup>2</sup> The common phenotypic consequences of duplications for different X chromosome segments can hardly be regarded as discrete effects of specific genes but may rather be ascribed to a supragenetic mechanism.

Most females with Xq duplications appear to be phenotypically normal but at least six previous cases have presented with developmental delay, congenital anomalies, short stature, or ovarian dysfunction.<sup>4</sup> The constant inactivation of the rearranged X chromosome documented in normal carriers as well as the opposite pattern found in one abnormal girl with a de novo duplication<sup>6</sup> and the data in our family argue for a simple correlation between gene expression of the duplicated segment and phenotype; furthermore, the preferential inactivation of the duplicated Xq chromosome also observed in most phenotypically abnormal carriers<sup>4</sup> may still agree with such a relationship as the inactivation pattern would vary among different tissues. Incidentally, the occurrence of short stature in some "normal" carriers<sup>4,13</sup> (present study) points to a wide clinical spectrum and is consistent with the aforementioned correlation. Additional support for the crucial role of the partial X disomy in the female phenotype comes from the severe clinical consequences of non-inactivated small ring X chromosomes<sup>17-19</sup> as well as from balanced X; autosome translocations whose significant association with mental retardation and congenital anomalies in female carriers has been related to functional disomy rather than to spreading of inactivation into the autosomal segment.<sup>20</sup>

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