Functional Xp disomy and de novo t(X;13)(q10;q10) in a girl with hypomelanosis of Ito

L S Correa-Cerro, H Rivera, A I Vasquez

Abstract
We report on a 16 month old girl with hypomelanosis of Ito and a balanced de novo (X;13)(q10;q10) translocation in which the der(Xp13q) had the X centromere (as assessed by FISH with the DXZ3 probe). A functional Xp disomy was shown in a small proportion of cultured lymphocytes by means of a BrdU terminal pulse. This observation supports the notion of a distinct form of hypomelanosis of Ito resulting from a functional Xp disomy. (J Med Genet 1997;34:161–163)

Keywords: hypomelanosis of Ito; X;autosome translocation; functional Xp disomy.

Hypomelanosis of Ito (HI) is characterised by hypopigmented whorls, streaks, and patches typically distributed along the lines of Blaschko; abnormalities of the central nervous, eye, and musculoskeletal systems have also been described. The observed HI of a 16 month old girl was a chromosome examination performed because of a previous abortion. Both parents and their three older children were normal; in particular, there was no family history of pigmentary anomalies. She was delivered at term by caesarean section because of pre-eclampsia; weight was 3.110 g, length 48 cm, and Apgar scores were 8 and 9 at one and five minutes respectively. At birth, streaky hypopigmented lesions were noted on the body. From 3 months of age she developed generalised tonic-clonic convulsions, which were unsuccessfully treated with phenobarbital. An EEG showed an abnormal generalised activity whereas a CT scan showed isodense zones in the frontal lobes. Ophthalmoscopic examination at 4 months showed nystagmus and hypoplasia of the fovea more apparent in the left eye. Physical examination at 16 months of age (fig 1) showed weight 10.5 kg (90th-97th centile), length 85 cm (above the 97th centile), OFC 44 cm (10th-20th centile), hypotonia, no head control, nystagmus, synophrys, upward slanting palpebral fissures, dysplasia of the teeth, widely spaced nipples, and irregular streaky hypopigmented lesions with a mottled, streaked, or whorled appearance on both sides of the trunk and the extremities; vesicobullous or verrucous lesions were not noted.

Radiographs showed brachycephaly, dorso-lumbar scoliosis, hypoplastic ischia, and an asynchronous accelerated bone age (pelvis 4 years, hands between 2 and 3 years).

Table 1  Hypomelanosis of Ito with X;autosome translocations

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Karyotype</th>
<th>X inactivation patterns in cultured cells</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>5 y</td>
<td>46,X,t(X;9)(p11.21;q33.2) de novo (L)</td>
<td>Normal X inactive in 100% of 21 cells (L)</td>
<td>8</td>
</tr>
<tr>
<td>F</td>
<td>15 y</td>
<td>46,X,t(X;9)(p11;q34) de novo (L &amp; S)</td>
<td>Normal X inactive in more than 90% of cells (L)</td>
<td>9</td>
</tr>
<tr>
<td>F</td>
<td>6 mth</td>
<td>46,X,t(X;14)(q11q13) de novo (L)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F</td>
<td>3 y</td>
<td>46,X,t(X;22)(q11.2q13.3) de novo (L)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F</td>
<td>3 y</td>
<td>46,X,t(X;18)(p11q23) de novo (L &amp; S)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F</td>
<td>12 mth</td>
<td>46,X,t(X;17)(q13p13) de novo (L &amp; T)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F</td>
<td>7 y</td>
<td>46,X,t(X;10)(p11q11) mat (L)</td>
<td>Normal X inactive in 100% of 50 cells (L)</td>
<td>13</td>
</tr>
<tr>
<td>F</td>
<td>21 y</td>
<td>46,X,t(X;17)(cen;cen) de novo (L)</td>
<td>Normal X inactive in 100% of 33 cells (L) and in 100% of 29 cells (normal and abnormal S)</td>
<td>14</td>
</tr>
<tr>
<td>F</td>
<td>16 mth</td>
<td>46,X,t(X;13)(q10q10) de novo (L)</td>
<td>Normal X inactive in 98.7% of all cells (L)</td>
<td>Present case</td>
</tr>
</tbody>
</table>

L = lymphocytes, T = tumour cells (plexus papilloma), S = skin fibroblasts.
facturer’s protocol (Oncor) with a digoxigenin labelled X centromere probe (DXZ3). The sites of hybridisation were visualised using either rhodamine labelled antidigoxigenin/DAPI or fluorescein labelled antidigoxigenin/propidium iodide. We observed the hybridisation signal on the normal X chromosome and on the der(Xp13q) chromosome (fig 2B). Therefore, the X breakpoint was assigned to q10. A cell line of this patient is not available.

Discussion

The balanced X;autosome translocations found in nine unrelated females with sporadic HI (table 1) exhibit some distinct characteristics, namely non-mosaic occurrence, a pericentromeric or centromeric X chromosome breakpoint, apparent randomness of the autosomes involved, and, apart from one case, a de novo origin. Therefore, these patients may constitute a distinct form of HI. The skewed X inactivation in the present case conforms to previous analyses in cultured cells8 9 14 (table 1), but the alternate pattern documented in a small proportion of cells confirms previous observations in either cultured lymphocytes1 or uncultured skin cells.14 As for the causative mechanism, the work of Hatchwell et al14 points to a mosaic Xp functional disomy rather than to a gene disruption, a conclusion supported by our findings. In fact, the six other translocations in which the X chromosome functional disomy was not assessed9 10 13 are consistent with this view, that is, the X chromosome breakpoint in all of them allows for the occurrence of the alternate inactivation pattern in which the derivative with the X inactivation centre is inactivated and so these cells are functionally disomic for Xp sequences. Since a functional non-mosaic Xp disomy does not result in a HI phenotype (for example, Gustashaw et al15), it may be inferred that Xp disomy, like other imbalances (triploidy, trisomy 18, and tetrasyomy 12p13), only causes such a phenotype when occurring in a mosaic state.14 Moreover, the absence of male patients with HI and a balanced X;autosome translocation, if not a random event, is in keeping with this, as X chromosome disomy cannot occur in them. The single inherited X;autosome translocation14 may be accounted for by a more stringent selection in the mother whose nearly normal phenotype facilitated the transmission of the translocation to her affected daughter.

According to the banding patterns, the present translocation was regarded as a whole arm exchange, yet FISH results indicated that the X chromosome breakpoint was outside the centromere. Hence, this rearrangement differs from the single true whole arm translocation associated with HI.14

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1 Ito M. Studies on melanin. XI. Incontinentia pigmenti achromians: a singular case of nevus depigmentosus

![Figure 1](http://jmg.bmj.com/)
The patient at 16 months of age. (A) Note synophrys and upward slanting palpebral fissures. (B) Irregular hypopigmented lesions on the dorsal aspect of the leg.

![Figure 2](http://jmg.bmj.com/)
(A) Partial G banded karyotypes showing the t(X;13)(Xp13q;Xq13p) in the patient; the derivatives are on the right in each pair. (B) Results after hybridisation with DXZ3 labelled with digoxigenin and detected with rhodamine labelled antidigoxigenin/DAPI. Note the signal on both the normal X and the der(Xp13q).
Hypomelanosis of Ito and t(X;13)

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