Germline duplication of chromosome 2p and neuroblastoma

Jatin S Patel, John Pearson, Lionel Willatt, Tony Andrews, Richard Beach, Andrew Green

Abstract
A child with a germline duplication of chromosome 2p, 46,XY,der(13)(2;13)(p23;q34), who developed a fatal neuroblastoma confirmed at necropsy is reported. Fluorescent in situ hybridisation studies showed chromosome 2p (p23-pter) duplicated on chromosome 13 (q34). The clinical features of the present case shared many similarities to previous reports of trisomy 2p and there have been two cases described with neuroblastoma. Germline duplication of chromosome 2p including the N-myc proto-oncogene may have predisposed to the development of neuroblastoma in this case.

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Keywords: trisomy 2p; neuroblastoma; N-myc

Neuroblastoma is the second commonest tumour of childhood with an age standardised rate of 7-12 per million and accounts for 6-10% of all childhood cancers.1 Eighty percent of cases are diagnosed before the age of 5 years and the mean age at diagnosis is 2 years.2 The tumour arises from primitive neural crest cells which form the adrenal medulla and sympathetic nervous system. Occasional cases have been described with germline cytogenetic rearrangements who have developed neuroblastoma. However, no consistent genetic syndrome has been recognised associated with neuroblastoma. Somatic cytogenetic abnormalities in neuroblastoma cells are common and these have suggested genetic loci important in neuroblastoma development.3

Partial trisomy 2p was first reported over 25 years ago.4 Lurie et al5 recently reviewed over 50 cases including three new reports. Characteristic clinical features included anomalies of the face, trunk, limbs, and genitalia, and psychomotor delay. Other congenital defects that appear to be associated with this trisomy involve the neural tube, lung, heart, and diaphragm. There have been two reports of neuroblastoma associated with partial trisomy of 2p.6 7

We report a child in whom an initial clinical diagnosis of partial trisomy 13 was made who subsequently developed a neuroblastoma and was retrospectively found to have a partial trisomy of chromosome 2p.

Case report and cytogenetic studies
A male child was delivered by forceps at 38 weeks' gestation following induction for growth retardation which had been present from 30 weeks' gestation. At birth the child weighed 2200 g (<3rd centile) and a number of abnormalities were noted. These included hypertelorism, micrognathia with a cup shaped mouth, low set, dysmorphic ears, and deformity of the rib cage. The hands were broad with long fingers and there was postaxial polydactyly of both hands and the left foot. A small area of skin aplasia affecting the posterior scalp and a small buried penis were also present. No clinical photographs are available. The parents were unrelated and white and had a 3 year old daughter who was well.

The clinical features were suggestive of a partial 13q trisomy and routine G banded chromosome analysis showed a male karyotype with extra material on the long arm of chromosome 13 (fig 1). Subsequent fluorescent in situ hybridisation (FISH) studies using a whole chromosome 13 paint indicated that the additional material was not chromosome 13 derived. Parental karyotypes were examined and no abnormality was detected, suggesting a de novo chromosome rearrangement in the child.

At the age of 5 months the child developed generalised seizures with hypsarrhythmia which remained unresponsive to treatment with steroids and anticonvulsants. Spontaneous periordial bruising with abdominal swelling appeared at the age of 17 months associated with a cosgulopathy suggestive of an occult malignancy. An abdominal ultrasound scan subsequently showed large masses in the region of both adrenal glands consistent with a neuroblastoma. In view of the child's multiple abnormalities conservative care was agreed with the family and death occurred after 48 hours. Permission was given for a limited postmortem biopsy of the abdominal masses which showed necrotic haemorrhagic tumour consistent with...
set ears, hyperextensible long fingers, and an ectopic anus. The child died at 5 weeks following ventilation for agenesis of the left lung. At necropsy, neuroblastoma in situ was found in random sections of one adrenal gland.

Nagano et al reported an infant who developed metastatic neuroblastoma affecting skin, liver, lung, and bone marrow at the age of 8 months. Multiple congenital anomalies were present including microcephaly, frontal bossing, hypertelorism, ptosis, micrognathia, and a buried penis. Karyotype analysis showed partial trisomy for 2p (p13–pter) which was paternally inherited. The child’s father, paternal uncle, and grandfather all carried the same reciprocal translocation, 46,XY,t(2;13)(p13;p11), and had congenital cataract and microphthalmos.

The term “neuroblastoma” describes developmentally related tumours arising from primitive neural crest tissue. These tumours may have an aggressive course refractory to treatment, spontaneous regression, or may mature into a benign ganglieneuroma. Somatic cytogenetic abnormalities in neuroblastoma cell lines are common and often involve chromosomes 2, 1, and 14.19 There have been a number of reports of constitutional chromosomal abnormalities and development of neuroblastoma although no consistent cytogenetic abnormality appears to be present (table 1). Cytogenetic studies of tumour cells from these patients have not been described.

Amplification of the N-myc proto-oncogene is a frequent finding in aggressive neuroblastoma cells. This amplification correlates with cytogenetic abnormalities described as extra-chromosomal double minutes (DMs) and homogeneous staining regions (HSRs).19 20 N-myc maps to chromosome 2 band p23-24 and FISH studies have recently shown that N-myc is occasionally duplicated at its resident site in neuroblastoma cell lines which lack amplification.21-26 This has suggested N-myc duplication may precede amplification or represent an alternative mechanism of N-myc activation. In the case presented, a germline duplication of 2p, giving rise to three copies of

Table 1: Reported cases of neuroblastoma with constitutional chromosomal anomaly

<table>
<thead>
<tr>
<th>Case</th>
<th>Authors</th>
<th>Chromosome(s) involved</th>
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<tbody>
<tr>
<td>1</td>
<td>Feingold et al27</td>
<td>Trisomy 13</td>
</tr>
<tr>
<td>2</td>
<td>Nevins et al28</td>
<td>Trisomy 13</td>
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<tr>
<td>3</td>
<td>Pegelow et al29</td>
<td>11, 21p</td>
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<tr>
<td>4</td>
<td>Moorhead and Evans30</td>
<td>4, 7 (balanced translocation)</td>
</tr>
<tr>
<td>5</td>
<td>Moorhead and Evans30</td>
<td>11,16 (balanced translocation)</td>
</tr>
<tr>
<td>6</td>
<td>Say et al31</td>
<td>46,XX,der(10)(q21.2;q21.2)</td>
</tr>
<tr>
<td>7</td>
<td>Nagano et al32</td>
<td>46,XX,der(10)(q21.2;q21.1)</td>
</tr>
<tr>
<td>8</td>
<td>Fryns et al33</td>
<td>46,XX,der(7)(q31.3;q31.3)</td>
</tr>
<tr>
<td>9</td>
<td>Sanger et al34</td>
<td>der(13)(p13.3;q14.2)</td>
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<tr>
<td>10</td>
<td>Qureshi et al35</td>
<td>der(10)(q10.3)(q21.2)</td>
</tr>
<tr>
<td>11</td>
<td>Koiffmann et al36</td>
<td>46,XY,der(11)(p11.2;q11.1)</td>
</tr>
<tr>
<td>12</td>
<td>Michalski et al37</td>
<td>t(1;2)(p21.2;q11.2)</td>
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<tr>
<td>13</td>
<td>Laureys et al38</td>
<td>t(1;7)(p36.1;q21.2)</td>
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*Case reported as “trisomy D” on unbandable karyotype but clinical description consistent with trisomy 13.
1Paracentric inversion of chromosome 11 and probable deletion of the short and long arm of chromosome 21.

Figure 2. FISH preparation using whole chromosome 2 paint indicating that the additional material on 13q is chromosome 2 derived.

Discussion

The clinical features seen in our case were initially suggestive of partial duplication of chromosome 13 (polyaactyly, long fingers, and scalp aplasia). In retrospect, several features are consistent with partial trisomy 2p, particularly the deformed rib cage and small penis. In the review by Lurie et al, consistent facial anomalies included prominent, high forehead with frontal upswEEP of hair, hypertelorism, short, broad nose, narrow palate, maxillary hypoplasia, small, low set ears, and micrognathia. Skeletal anomalies included dolicho-stenomelia, long, tapering fingers, and “fan-like” position of the toes. Genital findings included cryptorchidism, overriding scrotum, and small penis. The clinical manifestations of polyactyly and scalp aplasia have not been reported in previous descriptions of trisomy 2p.

Pfeiffer et al reported two patients with deletion of chromosome 13 (q34–qter) who have no clinical similarities to our case. Cleft palate and hypospadias were present in one patient and minor dysmorphic features in the other.

There have been two reports of neuroblastoma in association with partial trisomy of chromosome 2p. Say et al described a child with multiple congenital anomalies and duplication of 2p21-25. These included blepharophimosis, beaked nose, posteriorly rotated, low

a neuroblastoma. Further histological or cytogenetic studies were not performed.

In view of the association of 2p translocation and neuroblastoma formation, FISH studies were repeated. A whole chromosome 2 paint and the cosmid cloned probes CEB1/CEB11 and pNb101, which map to the subtelomeric region of the long arm and the NYMC proto-oncogene locus at 2p23 respectively, were used (fig 2). These studies showed that the chromosomal material attached to 13q was derived from the short arm of chromosome 2 (p23–pter) and there was an associated terminal loss of chromosome 13 giving a germline karyotype of 46,XY,der(13)(t(2;13)(p23;q34).

Discussion

The clinical features seen in our case were initially suggestive of partial duplication of chromosome 13 (polyactyly, long fingers, and scalp aplasia). In retrospect, several features are consistent with partial trisomy 2p, particularly the deformed rib cage and small penis. In the review by Lurie et al, consistent facial anomalies included prominent, high forehead with frontal upswEEP of hair, hypertelorism, short, broad nose, narrow palate, maxillary hypoplasia, small, low set ears, and micrognathia. Skeletal anomalies included dolicho-

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N-myc, as shown by FISH studies, may have predisposed to the development of neuroblastoma.

In conclusion, the infant we have described had clinical features consistent with a partial trisomy of chromosome 13q which was excluded by FISH with chromosome 13 paint. The subsequent development of a neuroblastoma suggested that the extra chromosomal material contained an oncogene and prompted FISH studies for chromosome 2p. The region (p23-24) which was translocated to chromosome 13 in our patient included the N-myc proto-oncogene which is involved in neuroblastoma development. We would suggest considering FISH studies with the N-myc probe in a person with an unidentified constitutional chromosomal rearrangement who develops a neuroblastoma.

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17. Michalski AJ, Cotter FE, Cowell JK. Isolation of chromosome specific DNA sequences from an Alu polymere chain reaction library to define the breakpoint in a patient with a constitutional translocation t(1;13)(q22;q12) and ganglionneuroblastoma. Oncogene 1992;7:359-67.