Interstitial deletion, del(4)(q12q21.1), owing to de novo unbalanced translocation in a 2 year old girl: further evidence that the piebald trait maps to proximal 4q12

Albert Schinzel, Christian P Braegger, Lukrecija Brecevic, Fabrizio Dutly, Franz Binkert

Abstract
A very short, microcephalic, and mentally retarded 2 year old girl showed minor anomalies including prominent occiput, delayed closure of the anterior fontanelle, high frontal hairline, prominent ears, upward slanting palpebral fissures, a small nose with bulbous tip, delayed tooth eruption and bone maturation, and short and tapering fingers and toes. She did not have a white forelock. Cytogenetic investigation disclosed a de novo unbalanced translocation between chromosomes 4 and 18 with deletion of 4q12–q21.1. Molecular investigation showed lack of a paternal allele for the microsatellite markers D4S392 and D4S398. This case shows indirect evidence that the piebald gene maps to proximal 4q12.
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Keywords: chromosome deletion 4q; piebald trait; unbalanced translocation

Interstitial deletion of the segments 4q11q21 or 4q12q21 has been reported in eight patients, five of whom showed the piebald trait, a white forelock. Beyond this rather unusual finding, they did not share a striking common pattern of dysmorphism and malformations.

We report clinical, cytogenetic, and molecular findings of another patient with an interstitial deletion of 4q12q21.1. She did not show the piebald trait and, in contrast to all but one of the previous cases, her deletion was secondary to a de novo translocation which had occurred in the paternal germline.

Case report
The proband, a girl, was the product of the first pregnancy of a 26 year old, healthy mother and her 33 year old partner. The mother worked as a waitress and smoked about 10 to 20 cigarettes a day throughout the pregnancy which was normal apart from a short period of gastrointestinal infection at the end of the first trimester. Delivery occurred one day before the expected term. At the end of labour, cardiotocography showed decreased fetal heart velocity, but at delivery there was only mild asphyxia. Birth weight was 2700 g and length was 45 cm. No special features were initially noticed in the infant and so she was discharged with her mother on day seven after delivery. Subsequently, she suffered from episodes of colicky abdominal pain and abdominal distension of unknown aetiology. Motor and mental development were delayed with sitting at 8 to 9 months and standing at 16 months.

Clinical examination at the age of 19 months showed length 68 cm (<3rd centile, approximately −4 SD), weight 7.5 kg (<3rd centile, approximately −3.5 SD), OFC 45.5 cm (3rd-10th centile). Clinical dysmorphological evaluation disclosed the following abnormalities: prominent occiput, anterior fontanelle still patent 2 × 2 cm, high frontal hairline, prominent ears (ear length 4.7 cm, below the 10th centile), upward slanting palpebral fissures, small nose with bulbous tip, delayed eruption of teeth (first at 18 months, at present only two lower and one upper incisor erupted), barrel chest, prominent abdomen, short and tapering fingers (total hand length 8.4 cm, below the 3rd centile), rocker bottom feet, and short and broad toes. On external examination, there were no other abnormalities; cardiac auscultation indicated a 1-2/6 systolic murmur which was considered to be only functional. No hypo- or hyperpigmented areas of the skin were visible.

Figure 1  Chromosomes 4 and 18 from one RFA and GTG banded metaphase each of the proband. Breakpoints are indicated by arrows on the normal homologues of the GTG banded karyotype and the diagram.
FURTHER INVESTIGATIONS
Histological analysis of a duodenal biopsy specimen showed ectatic vessels, but otherwise normal findings, and histological examination of a colonic biopsy showed normal findings. Thus, the gastrointestinal problems were considered to be the result of aerophagia.

Radiographs of the lumbar and sacral vertebral column and pelvis were normal. Hand x rays showed normal bones but severe delay in carpal (9/12) and phalangeal (12/12) bone ages at a chronological age of 24 months.

CYTOGENETIC INVESTIGATIONS
GTG and RFA banded metaphases from lymphocyte chromosome cultures showed an unbalanced translocation between chromosomes 4 and 18 with presumed loss of the segment (4q12→q21.1): 46XX,t(4;18) (4pter→4q12::18q23→18qter; 18pter→18q23 ::4q21.1→4qter) (fig 1). Chromosome painting with libraries of chromosome 4 (digoxigenised, red) and chromosome 18 (biotinilated, green) showed the reciprocity of the translocation and excluded involvement of a third chromosome (fig 2). Parental karyotypes were normal. No cell line of the proband is available.

MOLECULAR INVESTIGATIONS
The results of microsatellite marker analysis of loci within the segment 4q12→q21 are presented in table 1 and fig 3. Control markers at 4q26→q27 were analysed in order to exclude maternal uniparental disomy 4. For markers D4S392 and D4S398, the proband had inherited one of the two maternal alleles, but lacked either of the two paternal alleles; marker D4S399 was not informative. The three markers on distal 4q showed normal biparental inheritance in the proband. Thus, the combined results confirmed the interstitial deletion of proximal 4q, disclosed its paternal origin, and excluded maternal uniparental disomy of chromosome 4.

Discussion
Interstitial deletion of the segment 4q12→q21.1, as was found in the proband, has so far only rarely been reported. In one case reported in the early banding period (1977),\(^2\) the proximal breakpoint was determined at 4q11, while in five others,\(^1,1\) it was in 4q12. Owing to a less precise determination of breakpoints in the seventies, it is possible that the breakpoints did not differ and that the former case also had the proximal breakpoint at 4q12. Only in the four later cases was the distal breakpoint found to be within 4q21, specifically in its proximal segment, at 4q21.1\(^\text{1}\)\(^\text{1}\); 4q21.1 was also the breakpoint in our proband.

A comparison of the clinical findings in the eight previously reported patients with the proband of this report is presented in table 2.

<table>
<thead>
<tr>
<th>Primer</th>
<th>Locus</th>
<th>Alleles</th>
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<tbody>
<tr>
<td>D4S398</td>
<td>4q13-q21</td>
<td>d, cd, ab</td>
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<tr>
<td>D4S399</td>
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<td>a, aa, ab</td>
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<tr>
<td>D4S392</td>
<td>4q13-q21</td>
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<tr>
<td>D4S247</td>
<td>4q26-q27</td>
<td>ac, cc, ab</td>
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<td>D4S427</td>
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<tr>
<td>D4S175</td>
<td>4q26-q27</td>
<td>bc, cc, ab</td>
</tr>
</tbody>
</table>

The alleles are given in the order: paternal, mother, father. The markers showing paternal deletion are given in bold. Allele designations (a to d) are arbitrary.

Figure 2. Dual colour FISH of a metaphase of the proband (A) with GTG banded control (B). Chromosome 4 is painted in green, chromosome 18 in red. Note the reciprocal translocation with a large segment of chromosome 4 attached to chromosome 18 and a tiny segment of chromosome 18 attached to chromosome 4.
This analysis shows that, as is often the case in interstitial deletions,\(^a\) the pattern of abnormalities is not very striking and thus, in contrast to many terminal autosomal deletions with a rather abnormal phenotype, it would hardly be possible to recognise the specific deletion in such a patient from the clinical findings alone. However, if multiple minor anomalies and growth and mental retardation are present in a patient with a white forelock (piebald trait), the situation is different: the latter is a unique finding in chromosome aberrations,\(^b\)\(^c\)\(^d\) having been reported so far only in proximal deletions of 4q. Its occurrence in the first two cases\(^e\) was one of the reasons to refine the provisional mapping of the gene for the dominant piebald trait to the deleted region 4q12→q21.1. However, lack of a white forelock in 4/9 patients (including ours) with a deletion including 4q12→q21.1 leaves several explanations open. First, the proximal breakpoint could be different in the patients with and without a white forelock, being more proximal and thus including the “piebald gene” in the former group. Evidence for this explanation is a case with an overlapping, but more distal 4q deletion which includes the segment (4q13→q22) in which no features of the piebald trait were found.\(^f\) Second, a further controlling gene might be involved which would have two alleles of approximately equal incidence, restoring the effect of the deletion of the piebald gene if one of the alleles is present. This explanation is not very likely as it would imply that the penetrance of the piebald trait would be well below 50% which is not the case, at least not if associated findings (heterochromia of the iris, deafness, Hirschsprung disease, epitheliomas) are also considered.\(^g\)

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