Cytogenetic findings indicate heterogeneity in patients with blepharophimosis, epicanthus inversus, and developmental delay

Mette Warburg, Merete Bugge, Karen Brondum-Nielsen

Abstract
Three unrelated, mentally retarded boys with typical blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) were found to have chromosomal aberrations. One of them had a del(3)(p25), another patient had a de novo translocation t(2;3), which after high resolution banding combined with chromosome painting was interpreted to be unbalanced with a loss of band q23. The third patient had a del(7)(q34). The phenotypes of the two patients with chromosome 3 related syndromes were similar, but the third also had genital malformations resembling the Smith-Lemli-Opitz syndrome. This patient had a palatal ridge, and a single mesial maxillary tooth suggesting the holoprosencephaly sequence, but CT scans of the brain were normal.

(J Med Genet 1995;32:19–24)

The blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) is an autosomal dominant condition. The ears may be simple and owing to the shortness of the palpebral fissures, there is an increased inner canthal distance (ICD), that is, telecanthus. The outer canthal distance (OCD) is often normal. Two clinical types have been delineated: in type 1 there is reduced female fertility and early menopause, and in type 2 this is not the case.

We were interested in the chromosomal assignment of the BPES syndrome gene(s) and have searched the files of this eye clinic, which gives service to patients with developmental delay. We have found three patients with BPES and abnormal karyotypes.

Methods
The patients underwent a complete paediatric and ophthalmological examination including visual acuity with Teller cards or optotypes, motility, slit lamp examination, ophthalmoscopy, and evaluation of facial features. Routine chromosomal analyses were done with QFQ, GTG, and high resolution RBA banding.1 Chromosome painting using commercially available biotin-dUTP labelled chromosome specific libraries (Cambio) was performed according to the manufacturer's instructions. In brief, chromosomal slides were pretreated, dehydrated, and denatured before the application of the probe which had been denatured and preannealed. Hybridisation was carried out overnight at 42°C. Amplification of signals was done with avidin-FITC alternating with anti-avidin.

The fluorescent signals were viewed in a Zeiss Axioplan microscope equipped with appropriate filters and photographed. The chromosomes were counterstained with propidium iodide.

Chromosome paints of chromosomes 2 and 3 were used in case 2, and chromosome painting of chromosome 7 as well as a chromosome 7 specific telomeric probe (ONCOR) were applied in case 3.

Case reports
CASE 1 (280362)
This patient (fig 1A) has been described previously1 and we re-examined him when he was 31 years old. The parents were unrelated and healthy, and no similar case was known in the family. Four older and one younger sib were healthy. The mother was 36 and the father 41 years old at the birth of the patient; the mother had a radiographic examination of her stomach in the seventh week of pregnancy. The patient had epicanthus inversus, blepharophimosis, ptosis with ancillary function of the frontalis muscle when looking upwards, nystagmus, and left esotropia, and there was synophrys and telecanthus. The ICD was 48 mm, the OCD was 103 mm, and the palpebral fissure length was 25 mm (15th centile).

Visual acuity was 20/90, the right optic nervehead was mildly prominent, both corneas showed keratoconus, and there was a chorioidal coloboma at 6 o'clock in the left eye two disc diameters below the disc.

The external ear canals were narrow, the ears low set and posteriorly rotated; throughout childhood he had repeated middle ear inflamations. The occiput was flat and the forehead narrow; the occipitofrontal circumference (OFC) was 55.5 cm (normal) at the age of 31. The philtrum was long, the mouth was downturned, and the lips thin. There was pterygium colli and the skin was hyperextensible. The hands were broad and the fingers short, there was a supernumerary left fifth finger, and bilateral rocker bottom feet. The patient has epilepsy, and is moderately retarded. A CT scan was normal. The karyotype (fig 1B) was 46,XY,del(3)(qter→p25.3.).

CASE 2 (120973)
The mother was 23 and the father 28 years old at the birth of the patient. The paternal...
grandfather had cleft lip and palate, but otherwise the family was healthy. Pregnancy was uncomplicated and delivery was by caesarian section because of cardiac decelerations. Birth was at 37 weeks of gestation. Birth weight was 2000 g, length 43 cm, and OFC 30 cm. He was followed from the ages of 1 to 17 years (fig 2A). We found blepharophimosis, ptosis, and epicanthus inversus, a bifid uvula, retro-micrognathia, low set, posteriorly rotated ears, VSD, deficiencies of the skull, and short upper extremities with ulnar deviation of the second
Cytogenetic findings indicate heterogeneity in patients with blepharophimosis, epicanthus inversus, and developmental delay

Figure 3  FISH analysis of case 2 using a chromosome 3 specific library as probe (yellow signal). The chromosomes are counterstained with propidium iodide (red). The small arrow indicates der(3) where the paint extends approximately to q22. The large arrow indicates der(2) with the translocated part of chromosome 3q24qter.

Figure 4  Case 3. (A) The patient at 20 years of age; he had blepharophimosis, ptosis, and epicanthus inversus. (B) Karyotype of case 3 showing del(7)(pter→q34).
Clinical features in the del3p25 and 3q23 syndrome

<table>
<thead>
<tr>
<th>3p25&lt;sup&gt;−&lt;/sup&gt;</th>
<th>3q23&lt;sup&gt;−&lt;/sup&gt;</th>
<th>Our cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>Face</td>
<td>1</td>
</tr>
<tr>
<td>P toes</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Blepharophimosis</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Synophrys</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Epicanthus inversus</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Prominent forehead</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Thin upper lip</td>
<td>☐</td>
<td>(☐)</td>
</tr>
<tr>
<td>Downturned mouth</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Malformed ear</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Low set ears</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Triangular face</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Cataract</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Skull defects</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Skeletal anomalies</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Syndactyly</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Cleftdactyly</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Contractures</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Prominent heel</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Systemic anomalies</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>GI anomalies</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Renal cysts</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Retarded growth</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>High mortality in infancy</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
+ = presence of the sign, 0 = absence, and ND = not described.

Discussion

The BPES is an autosomal dominant disorder and clinically two types have been delineated: in type 1 there is female infertility, while this is absent in type 2, suggesting that type 1 is a candidate for a contiguous gene syndrome. The phenotypes are similar in the two types, blepharophimosis and ptosis being the most conspicuous signs, associated with a flat and broad nasal bridge, wrinkled forehead, epicanthus inversus, and antverted, rotated ears. Only type 1 has ovarian failure and early menopause.

Cytogenetically two different deletions on chromosome 3 have been described in patients with BPES: 16 patients with deletions of band p25.3 on the short arm<sup>17</sup> and 11 patients with deletions of bands q23-25<sup>6,14</sup> The critical region was considered to be 3q23<sup>7,14</sup> The phenotypes described in the two cytogenetic types are shown in the table.

Our cases 1 and 2 have classical BPES syndromes, with blepharophimosis, ptosis, epicanthus inversus, a depressed and broad nasal bridge, and telecanthus. Both had ocular colobomas; in case 1 this was a choroidal and in case 2 an iris coloboma. The ears were low set and posteriorly rotated. Case 1 had keratoconus, the external ear canals were narrow, and he also had unilateral postaxial polydactyly, while case 2 had defects of the cranial bones. Case 1 had a deletion of 3p25 while case 2 was considered to have a deletion of 3q23. The application of chromosome painting in case 2 shows that FISH analysis can be of diagnostic or counselling cytogenetic interest in resolving karyotypes. The banding pattern initially suggested a balanced translocation, but the chromosome painting was in favour of an unbalanced translocation bringing about a deletion proximal to 3q25. We then did a blinded revision of the high resolution R banding karyotype which supported the FISH findings. This further indicates that the critical region for BPES is 3q23.

Case 3 had blepharophimosis, epicanthus inversus, and ptosis. His ocular malformations were similar to those previously described in the BPES. He had hypospadias, a bifid preputium, and a curved penis. These malformations together with ptosis suggested to us for several years that he had the Smith-Lemli-Opitz (SLO) syndrome, but the parents would not allow supplementary examination of cholesterol metabolism. However, he also had features not associated with this syndrome. These were a bifid uvula, a palatal ridge, right atresia and left stenosis of the choanae, and a mesial tooth indicating HPE, features not associated with either BPES or SLO. He is alive at the age of 20 years and is moderately retarded. This is of the long arm of chromosome 7 with a breakpoint at band (7)(q34). The karyotype (fig 4C) was 46,XY,del(7)(pter→q34). FISH analysis showed chromosome 7 centromeric as well as telomeric signals on the normal and the deleted chromosome. A small cryptic telomeric translocation can thus be excluded (data not shown).
patient had a deletion of 7q34.

There is one other family on record in which two sibs, monosomic for 7q34, showed signs of the SLO syndrome. One causative factor was a translocation t(7;17)(q34;p13.1). A male child in this family had a 46,XY,−17, +der(17)(7;17)(q34;p13.1) karyotype and a Miller-Dieker phenotype. His four male cousins had a 46,XY,−7, +der(7)(7;17) (q34;p13.1) karyotype and showed clinical syndromes suggesting SLO.15 They had microcephaly, a deep nasal bridge, epicanthus, large ears, hypoplasia, microgenital, large renal cysts, congenital heart disease, overriding toes, thin ribs, and sacral malformations. One child survived and he had no blepharophimosis, ptosis, or epicanthus inversus. Our patient is much less impaired, but his dead sister and cousin had congenital renal cysts.

Holoprosencephaly (HPE) has been described in patients with deletions of 7q36, and patients with ring 7 with a breakpoint at 7q36 have shown cyclopia or cephobia, but less severe phenotypes have also been described.16-19 Thus, it has been known since the description of DeMyer et al20 that HPE may present facial anomalies without macroscopically abnormal brains. Although Cohen21 states that “the single maxillary incisor is nonspecific; it may occur on occasion as a striking microform of HPE, ... but it may also occur as an isolated abnormality as well in various other disorders”, we believe that the deletion of 7q34, a palatal ridge, and a single maxillary incisor is sufficient for establishing a diagnosis of the HPE sequence. The clinical features in our patient showed similarities to those in three patients with translocation breakpoints at 7q36 described by Krauss et al22 and Hatziioannou et al.23 They had absent incisors, with only a single mesial maxillary tooth, midline facial clefts, hypoplastic nasal bones, and microcephaly. Similarly, Taysi et al24 described a patient with a deletion of 7q34 and a normal brain CT scan, who had a single mesial tooth as the only sign of HPE. In the case of Madsen et al25 who had a del(7)(q34), maxillary incisor anlagen were absent, and the two mesial teeth were of abnormal shape.

In HPE there is a flat nasal root, but blepharophimosis and ptosis have not been described in patients with deletions of 7q34-36. In the patients described by Taysi et al24 and Madsen et al,25 the root of the nose was also flat and the pictures probably illustrate epicanthus inversus.

Ocular malformations in patients with deletions of the terminal part of the long arm of chromosome 7 include colobomas and microphthalmos,26 but such malformations are non-specific and may present in patients with deletions and duplications of almost all chromosomes.28 In this series, colobomas were observed in the patients with del(3p) and t(2;3).

Conclusion

BPES is a rare phenotype. We found three patients in whom BPES was associated with chromosomal anomalies out of more than 7000 retarded persons on file at the eye clinic. We can confirm that there are two locations on chromosome 3 which may give rise to the BPES syndrome, and that the phenotypes are fairly similar, and it is not known if they correlate with the clinical types, that is, if both or only one of them may be associated with ovarian failure. If ovarian failure associated with BPES were assigned to only one of the two loci, then it might still be possible that the phenotype results from a contiguous gene defect as suggested by Smith et al.29 It was unexpected that the facial phenotype in a patient with a deletion 7q34 was similar to the BPES. The patient also had genital and other anomalies similar to the SLO syndrome; our findings thus confirm that a phenotype similar to the SLO phenotype may occur in deletions of 7q34.

It is possible that our patient has a contiguous gene defect comprising loci for (at least) one type of blepharophimosis, an SLO phenotype, and HPE.

Blepharophimosis has been classified in two clinical types; this study has confirmed that it is also a genetically heterogeneous disorder.

This paper is dedicated to Margareta Mikkelsen on the occasion of her 70th birthday.

References

Cytogenetic findings indicate heterogeneity in patients with blepharophimosis, epicanthus inversus, and developmental delay.

M Warburg, M Bugge and K Brøndum-Nielsen

doi: 10.1136/jmg.32.1.19

Updated information and services can be found at:
http://jmg.bmj.com/content/32/1/19

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/