Holoprosencephaly and sacral agenesis in a fetus with a terminal deletion 7q36→7qter

Nicole Morichon-Delvallez, Anne-Lise Delezoide, Michel Vekemans

Abstract
We describe here a fetus with holoprosencephaly and signs of caudal deficiency sequence. Chromosome examination showed a de novo balanced reciprocal translocation (7;22) (q36;q11) with loss of the derivative chromosome 22 in 50% of the cells examined. The present report and available published data indicate that the terminal region of the long arm of chromosome 7 contains genes implicated in the development of the central nervous system and the caudal region.

Among chromosomal abnormalities associated with holoprosencephaly, aberrations of chromosomes 13 and 18 are the most common. There is, however, a long list of other numerical and structural chromosomal abnormalities in which holoprosencephaly may be found. For example, several reports associating holoprosencephaly with a terminal 7q deletion suggest that a putative locus for holoprosencephaly resides at or near 7q36. We describe here another patient with a translocation involving chromosome 7 and chromosome 22 whose malformations included holoprosencephaly and sacral agenesis.

Case report
Abnormalities of the fetus were first detected on ultrasound at 23 weeks' gestation. The skull was filled with fluid, leaving only a thin layer of brain tissue, and the corpus callosum was absent. There were no midline structures. After counselling the parents decided to terminate the pregnancy. Examination of the still-born male fetus showed microcephaly with cebocephaly and hypotelorism, right exophthalmia, low set and abnormally shaped ears, and micrognathia (fig 1). In addition the fetus had caudal agenesis. At necropsy, the following features were found: semilobar holoprosencephaly with a single dilated ventricle (fig 2), arhinencephaly, hypoplasia of the optic nerve, bilateral microphthalmia, and a right cataract. No congenital heart defect or hypoplasia of the thymus were noted. Radiological examination showed brachymesophalangism of the fifth finger, hypoplasia of the fifth lumbar vertebra, and absence of the sacral vertebræ (fig 3). The family history was unremarkable, there was no consanguinity, and the 30 year old mother was not diabetic. A previously born 4 year old boy was healthy.

CYTOGENETIC STUDIES
Fibroblast cultures from a lung specimen from the fetus were studied with standard RTB banding; 50% of the cells examined carried a balanced reciprocal translocation 46,XY,

Figure 1  Face of the proband at 24 weeks of gestation, showing cebocephaly (hypotelorism, monorchid, microstomia).

Figure 2  Holoplastic brain of the fetus. Dorsal view.
was normal. A fibroblastic cell line of the patient is available in our laboratory.

**Discussion**

Since the first case of a long arm deletion of chromosome 7 reported by de Grouchy et al.,
numerous authors have described similar deletions. This has allowed the delineation of a
syndrome including numerous non-specific
facial signs such as microcephaly, prominent
forehead, cleft lip and palate, bulbous nasal tip
with broad nasal bridge, hypertelorism, auricular
malformation, micrognathia, abnormal
genitalia in males, developmental delay, and
pre- or postnatal growth retardation. Holo-
prosencephaly has rarely been reported.6

The association of terminal 7q deletion with
developmental anomalies of the prosenceph-
alon has been well documented (table). Hat-
zioanannou et al.7 re-examining the family de-
scribed by Krauss et al.27 where a reciprocal
translocation (7;9) was segregating, found
minor signs of holoprosencephaly in three members. Two were carriers of the unbal-
anced chromosomal complement resulting in a
deletion of the 7q36→qter region, but one
carried an apparently balanced translocation.
From these data, Hatziioannou et al.7 con-
cluded that a putative locus for holoprosen-
cephaly resides at or near 7qter.

Interestingly, the 7q deletions associated
with holoprosencephaly mostly resulted from a
malsegregation of an inherited transloca-
tion,17 18 10 12-15 whereas deletions occurring de
novo are often associated with minor forms or
absence of holoprosencephaly. These findings
emphasise the importance of the telomeric
region of the long arm of chromosome 7
(7q36→7qter) in preventing the occurrence of
holoprosencephaly.

The present fetus with an apparently
balanced de novo reciprocal translocation
between chromosomes 7 and 22 had two major
anomalies: semilobar holoprosencephaly and
partial sacral agenesis. Fifty percent of the
cells had, however, an unbalanced chromoso-
mal complement resulting from a loss of the
derivative chromosome 22 (22pter→22q11).
Whether this event occurred early during
embryogenesis is difficult to establish as no
other fetal tissue could be examined.

Cytogenetic analysis of patients with Di
George syndrome has shown that unbalanced
translocations leading to monosomy 22pter→
22q11 are particularly common.18 In addition,
Scambler et al.19 showed that Di George syn-
drome can be associated with submicroscopic
deletions of the 22q11 region. Also, Back et al.20
described holoprosencephaly and arhinence-
cephaly in a fetus with an unbalanced reciprocal
translocation (11;22) with partial monosomy of
chromosome 22 (pter→q11). The proximal
position of the breakpoint observed in the
translocation carried by our fetus presumably
explains the absence of signs associated with
Di George syndrome.

We conclude therefore that one of the break-
points of the translocation (at 7q36) is respon-
sible for the holoprosencephaly observed in

---

**Figure 3** Radiographic appearance of the lower part of the spine: abnormally low number of sacral vertebral bodies which are less developed and irregular.

**Figure 4** R banded partial karyotype of the fetus showing the balanced reciprocal translocation (7;22) and the loss of der(22) in 50% of cells examined.
### Association of terminal 7q deletion with developmental anomalies of the prosencephalon and the caudal region.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>t(7;22) (q36;q21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(7) (q32→qter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(11;21) (p21;q36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(7) (q32→qter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>der(7) t(7;17) (q34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>der(7) t(7;18) (q34;q21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>der(7) t(3;7) (p23;q36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>der(7) t(7;8) (q36;p12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rec(7) inv(7) (p22;q34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>der(7) t(4;7) (q31;q36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>der(7)t(5;7)(q33;q34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Holoprosencephaly</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclopia</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proptosis</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroureter</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypospadias</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imperforate anus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacral agenesis</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single umbilical artery</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
our patient. Two hypotheses might be considered: either a loss of function of the gene at the breakpoint level or monosomy for the genes located on the terminal segment 7q36→7qter.

In addition, there is also some evidence to suggest that genes in this region might be implicated in the development of the caudal region. For example, in 1988, Schrander-Strumpel et al.11 described a boy with a terminal deletion 7q (7q32→7qter) and partial sacral agenesis. They found four other cases with a terminal deletion of chromosome 7q and various signs of caudal deficiency sequence11,22, and postulated that the caudal deficiency sequence was part of this chromosomal syndrome. Similarly, in 15 cases where a terminal deletion of the long arm of chromosome 7 was associated with holoprosencephaly, signs of caudal deficiency sequence were found in nine.

In conclusion, we suggest that the terminal region of the long arm of chromosome 7 contains genes implicated in the development of the central nervous system and the caudal region.

The authors thank Stéphane Loison and Marie-Pierre Pinson for their expert technical support and Michèle Le Drèvès for typing the manuscript.