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 stillborn male fetus showed microcephaly with cebcephaly 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 vertebrae (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,
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,7 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.34 Holoprosencephaly has rarely been reported.8

The association of terminal 7q deletion with developmental anomalies of the prosencephalon has been well documented (table). Hatziioannou et al1 re-examining the family described by Krauss et al17 where a reciprocal translocation (7;9) was segregating, found minor signs of holoprosencephaly in three members. Two were carriers of the unbalanced chromosomal complement resulting in a deletion of the 7q36→qter region, but one carried an apparently balanced translocation. From these data, Hatziioannou et al8 concluded that a putative locus for holoprosencephaly resides at or near 7qter.

Interestingly, the 7q deletions associated with holoprosencephaly mostly resulted from a malsegregation of an inherited translocation,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.1

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 chromosomal complement resulting from a loss of the derivative chromosome 22 (22p→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 22p→22q11 are particularly common.18 In addition, Scambler et al19 showed that Di George syndrome can be associated with submicroscopic deletions of the 22q11 region. Also, Back et al20 described holoprosencephaly and arhinencephaly 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 breakpoints of the translocation (at 7q36) is responsible for the holoprosencephaly observed in

![Figure 3](image3.png) Radiographic appearance of the lower part of the spine: abnormally low number of sacral vertebral bodies which are less developed and irregular.

![Figure 4](image4.png) R banded partial karyotype of the fetus showing the balanced reciprocal translocation (7;22) and the loss of dere(22) in 50% of cells examined.
Association of terminal 7q deletion with developmental anomalies of the prosencephalon and the caudal region.

<table>
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<tr>
<th>Karyotype</th>
<th>Present study</th>
<th>Schwartz et al (^1)</th>
<th>Kurtzman et al (^2)</th>
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<th>Schinzel (^\text{10}\text{11})</th>
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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. 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 sequence 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.

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