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Brief Clinical Report: Duplication 3p21→3pter and Cyclopia

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We report on a patient with an interchromosomal duplication of 3p, from 3p21 to 3pter, which apparently arose de novo. The infant had multiple malformations including holoprosencephaly and cyclopia. It is possible that duplication 3p has a generalized effect on the holoprosencephalon or the cleavage of the embryonic forebrain. Fibroblasts from the patient are available from the NIGMS Human Genetic Mutant Cell Repository (GM 7216).

Key words: chromosome 3, cyclopia, holoprosencephaly

INTRODUCTION

First described by Rethore et al [1972], duplication of a segment of chromosome 3p is relatively uncommon. Among approximately 20 cases observed [Pope et al, 1979; Suzumori et al, 1983; Gimelli, 1985, reviewed by Martin and Steinberg, 1983], most subjects had cardiac defects, gastrointestinal and urinary tract malformations, genital abnormalities, and craniofacial malformations, primarily of midline structures. Martin and Steinberg [1983] reported holoprosencephaly in one subject with dup(3)(p25→pter). Gimelli et al [1985] reported a patient with dup(3)(p2→pter) and cyclopia. Here we describe a second patient with dup(3)(p21→pter) whose malformations included holoprosencephaly and cyclopia.

CLINICAL REPORT

This 1,112 g female was delivered at approximately 30 weeks gestation of a 22-year-old, gravida 2, para 1 mother from a pregnancy complicated by polyhydramnios. The craniofacial malformations were suspected by prenatal ultrasound examination. The mother had used alcohol and "street drugs" during her pregnancy. After delivery

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the infant had Apgar scores of 2 and 1, at 1 and 5 min, respectively, had a few gasping respirations, and died 56 min after birth.

The infant had a single umbilical artery and cyclopia (Fig. 1). A single proboscis protruded above a midline diamond shaped palpebral fissure containing a single globe. The mouth was small, and the ears were rounded and slightly low-set. The anterior hairline extended almost to the proboscis and orbit, and there was hirsutism of the head, back, and shoulders. Polydactyly was not present.

The cerebrum consisted of a single V-shaped, nonconvoluted mass undivided into hemispheres, with corpus callosum, septum pellucidum, and olfactory apparatus all absent. The lining of the single dilated ventricle merged into a membrane lying adjacent to the dura, forming a large fluid-filled sac above and behind the fused cerebral hemispheres. The other viscera were normal.

CYTOGENETIC STUDIES

Fibroblast cultures (National Institute of General Medical Sciences GM7216) from third trimester amniotic fluid cells and skin and cartilage specimens of the propositus were studied with standard GTG-banding (Fig. 2). All cells carried a 7q+ marker chromosome identified as der(7),t(3;7)(p21;q36). The net result was an interchromosomal duplication of 3p21→3pter. Peripheral lymphocytes of both parents were normal with GTG-banding. Since formal paternity studies were not done, the possible origins of the der(7) include a de novo mutation, or adjacent I segregation of a t(3;7) with nonpaternity or with either parent being a mosaic for the translocation.

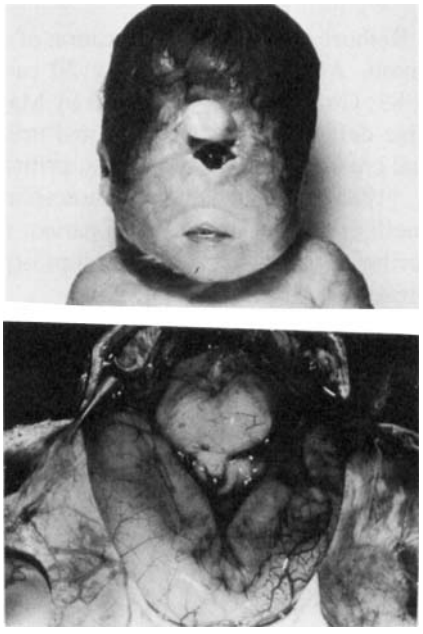

Fig. 1. Monocular or synophthalmic form of alobar holoprosencephaly with proboscis: clinical view and corresponding malformation.

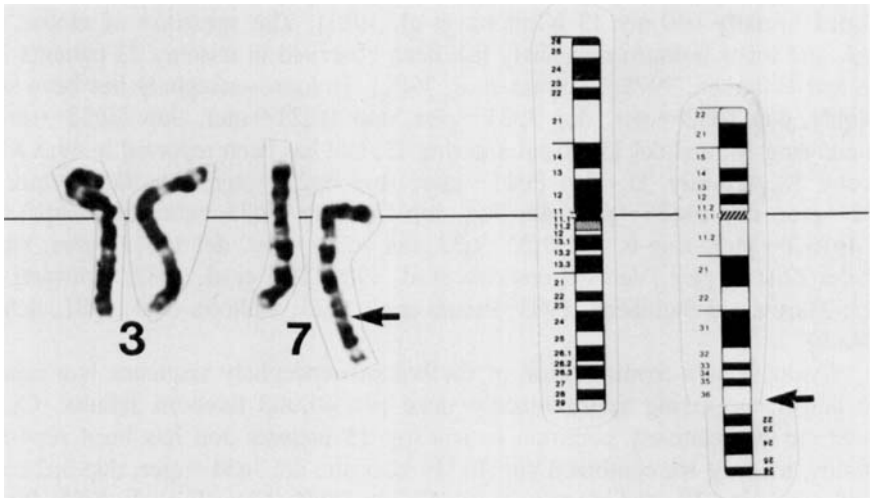

Fig. 2. The karyotype of the proposita was 46,XX,-7,+der(7),t(3;7)(p21;q36). Depicted are the normal chromosome pair 3, the normal 7, and the derived 7. The idiogram depicts a normal chromosome 3 and the derived 7, with the segment 3p21→3pter attached to distal 7q.

DISCUSSION

The "duplication 3p syndrome" has been described as including microcephaly, "square facies," temporal indentation, frontal bossing, hypertelorism or telecanthus, down-turned corners of the mouth, micrognathia, and short neck. The holoprosencephaly sequence with hypotelorism has been described [Martin and Steinberg, 1983] and includes arrhinencephaly [Van Regemorter et al, 1981] and cyclopia [Gimelli et al, 1985]. Both of the patients with cyclopia and the patient with arrhinencephaly had relatively large duplications extending from 3p21→3pter, and the patient who was described as having holoprosencephaly with hypotelorism had a smaller defect: dup(3p25→3pter). The observation of several patients having the defects of the holoprosencephaly sequence suggests that duplication 3p may interfere with this developmental field. The presence of heart defects, cleft lip and palate, meningocele, and hypospadias in patients with duplication 3p [Schinzel, 1984a] is consistent with a generalized effect on the midline developmental field [Shapiro, 1983; Opitz and Gilbert, 1982].

Holoprosencephaly can arise from defective induction of the precordial plate, causing failure of the prosencephalon to differentiate into the telencephalon and diencephalon. This normally occurs during the 4th to 5th week of embryogenesis, concurrent with facial development around the primitive mouth or stomodeum. The mesoderm of the face is in intimate association with the developing brain and is derived in part from neural crest cells. Holoprosencephaly can be thought of as a spectrum including alobar holoprosencephaly with cyclopia to semilobar holoprosencephaly with orbital hypotelorism and cleft lip, arrhinencephaly, and single central incisor [DeMeyer et al, 1964; James and Van Leeuwen, 1970; Smith and Jones, 1982].

Perhaps two-thirds of all holoprosencephalies are due to chromosome abnormalities, usually trisomy 13 [Gullotta et al, 1981]. The spectrum of alobar, semilobar, and lobar holoprosencephaly has been observed in trisomy 13 patients [Colacino and Pettersen, 1978, Gullotta et al, 1982]. Holoprosencephaly has been seen in triploidy, dup 1q32→qter, dup 3p25→pter, dup 11q21→qter, dup 13q22→qter, del 18p and ring 18, and del 13q distal and ring 13; and has been reported in 49,XXXXY, trisomy 18, trisomy 21, dup 3q21→pter, dup 6p22→pter, dup 6q21→qter, dup 9p22→pter, dup 14q24→pter, dup 16q, dup 17p, dup 17q23→qter, dup 22q13→qter, del 4p16.1→pter, ring 6, del 7q22→q32, del 7q32→qter, del 10p13→pter, ring 15, and del 22q11→pter [Van Regemorter et al, 1981; Hill et al, 1982; Schwartz et al, 1983; Martin and Steinberg, 1983; Roach et al, 1975; Gullotta et al, 1981; Schinzel, 1984a,b].

Cyclopia as a manifestation of the holoprosencephaly sequence is a relatively rare defect, occurring approximately once per 40,000 liveborn infants. Cyclopia appears to be relatively common in trisomy 13 patients and has been reported in triploidy, trisomy 18, combined dup 1q32→qter and del 7q34→qter, dup 3p21→pter, del 18p and ring 18, and monosomy G [Cohen, 1966; Gimelli et al, 1985; Roach et al, 1975; Schinzel, 1984b, 1986; Smart et al, 1986]. As expected, many of the same chromosomal defects are associated with holoprosencephaly without cyclopia. Probably any of the chromosome defects associated with holoprosencephaly can produce cyclopia.

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