

Further Delineation of the dup(3q) Syndrome

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Three patients with duplication of 3q regions ranging from 3q25→qter to the entire long arm provide additional documentation of the dup(3q) malformation syndrome. Data on 40 cases now reported define a characteristic face with hirsutism, synophrys, broad nasal root, anteverted nares, downturned corners of the mouth, micrognathia, and malformed ears recognizable even in the 30-week fetus and distinct from that of the Brachmann-de Lange syndrome. Other characteristic anomalies include congenital heart anomalies involving primarily septal defects, hand malformations including simian creases, abnormal dermatoglyphics, clinodactyly or camptodactyly, omphalocele, skeletal anomalies, and genitourinary malformations. Severe mental and growth retardation are common in those patients (64%) who survive the first year. Chromosome study of relatives is extremely important for counseling because only 10 of 40 cases represented de novo duplications.

Key words: dup(3q), multiple congenital anomalies/mental retardation (MCA/MR) syndrome

INTRODUCTION

Duplication 3q syndrome was first reported as "familial de Lange syndrome with chromosomal abnormalities" by Falek et al [1966] before banding studies associated duplication of the 3q21→3qter region with a distinctive phenotype [Hirschhorn et al, 1973; Boué et al, 1974; Allderdice et al, 1975]. The latter cases also had del(3q25→pter) due to segregation of a pericentric inversion, but the phenotype of isolated dup(3q) is virtually identical, as first documented by Chiyo et al [1976] and reviewed by Steinbach et al [1981]. The mild manifestations of isolated del(3p) [Wilson et al, 1982] are apparently obscured in the phenotype del(3p)/dup(3q). Although a previous report of two dup(3q) patients from our laboratory [Wilson et

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al, 1978] emphasized the resemblance of dup(3q) syndrome to the Brachmann-de Lange syndrome, there is no question that these syndromes are separate entities with distinctive facial changes and malformation patterns [Francke, 1978; Francke and Opitz, 1979]. Here we report three additional cases of the dup(3q) syndrome including one with duplication of the entire long arm.

CLINICAL REPORTS

Patient 1

This male infant was born at term after an uncomplicated pregnancy to a 22-year-old gravida 2, para 1 white woman. The father was 23 years old, and the family history was unremarkable. Measurements at birth included a weight of 1,870 gm, length 42 cm, occipitofrontal head circumference (OFC) 32 cm (all <3rd centile), and an interpupillary distance of 4.0 cm (50th centile). The infant (Fig. 1A,B) had a broad nasal root, right epicanthal fold, anteverted nares, long upper lip with flat philtrum, thin vermilion border of upper lip, downturned corners of the mouth, micrognathia, posteriorly augmented malformed ears with preauricular dimples, dysplastic corneal bands with irregular pupillary margins, cataracts, and highly arched palate due to hypertrophic lateral palatine ridges. The neck appeared short with pterygium colli. The thorax was flattened with the appearance of widely spaced

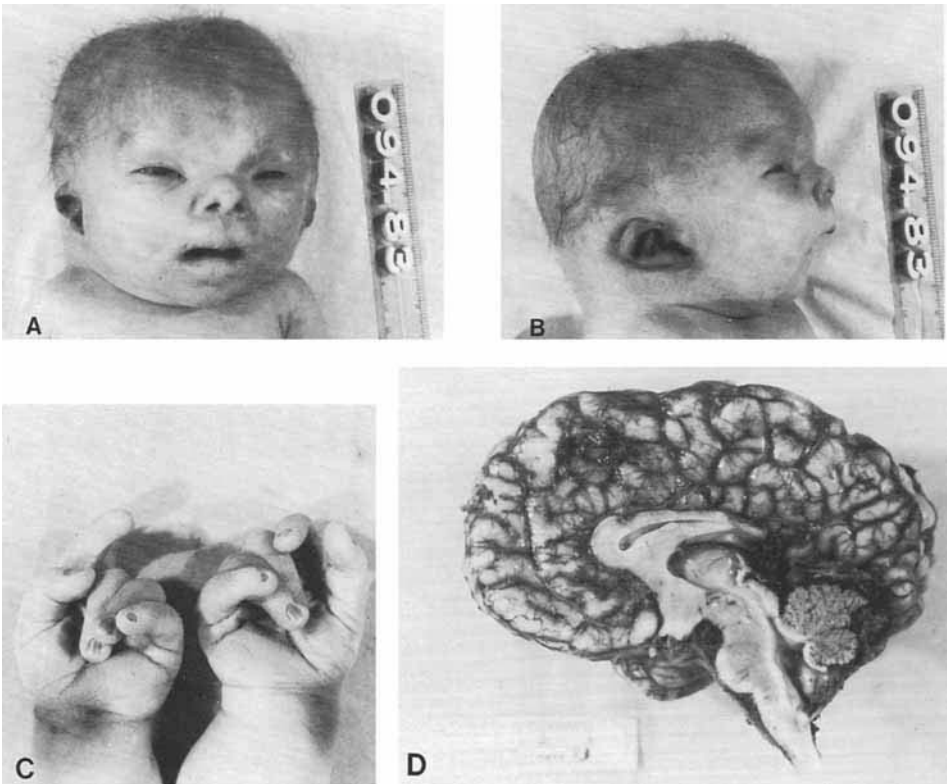


Fig. 1. Frontal view (A), lateral view (B), hands (C), and sagittal midline view of the brain (D) of patient 1.

nipples, but the interareolar distance was normal. Multiple cardiac defects—double outlet right ventricle, subaortic ventricular septal defect, aortic insufficiency, atrial septal defect—with pulmonary artery hypertension and persistent transitional circulation were documented by cardiac catheterization. There was a small abdominal omphalocele, diastasis recti, and bilateral cryptorchidism. There was a single palmar crease on the left, camptodactyly (Fig. 1C), hypoplastic nails, and dermatoglyphic arch patterns on fingertips. Skeletal survey demonstrated hypoplastic first ribs, absent twelfth ribs, and short sternum.

Apgar scores were 2 and 4 at birth; thereafter the child deteriorated progressively despite intubation, respirator, and Dopamine therapy. An initial platelet count was 21,000 but rose to 269,000 after antibiotic therapy. Results of other routine hematologic and blood chemistry studies and of a TORCH screen were normal. Death occurred at 14 hr; autopsy findings included thymic and pulmonary hypoplasia, splenomegaly, double left renal arteries, and a globular pancreas. Brain anomalies (Fig. 1D) included polymicrogyria, hypoplastic olfactory bulbs, elongated optic nerves, and increased hindbrain-midbrain angulation. Cytogenetic studies (see Fig. 4A) showed duplication of the 3q11→3qter region due to segregation of a maternal reciprocal translocation 46,XYt(3; 15)(q11; p11).

Patient 2

This male infant was electively terminated at 30 weeks of gestation by a 25-year-old white woman who had had a prior 10-week spontaneous abortion. The father was 27 and the family history was otherwise unremarkable. An ultrasound study at 26 weeks had shown bilateral fetal pleural effusions with lung hypoplasia and marked scalp, neck, and thoracic edema. A transabdominal fetal thoracentesis did not improve lung expansion but yielded the karyotype shown in Figure 4B. Autopsy findings included a length of 40.5 cm (50th centile), weight of 1.84 kg (>97th centile), OFC of 30 cm (80th centile), an abnormal face (Fig. 2A) with hypertrichosis, synophrys, broad nasal root, anteverted nares, long upper lip, and downturned corners of the mouth; short neck with edema of the nape; U-shaped cleft of the soft palate and micrognathia; broad-appearing chest with normal interareolar distance; ventricular septal defect with an aberrant right subclavian artery; ambiguous genitalia (Fig. 2B) with a small phallus, hypospadias, absent scrotal folds, and testes in the inguinal canals; bilateral simian creases with hyperconvex clubbed nails; abdominal ascites with an enlarged spleen and a centrally placed liver; bilateral calcaneovalgus deformity with rocker-bottom feet and prominent heels; and a normal-sized brain without gross malformation.

Chromosome study from the pleural fluid (Fig. 4B) showed duplication of the 3q25→3qter region due to segregation of a paternal reciprocal translocation 46,XYt(3; 13)(q25; q32).

Patient 3

This 5-month-old female was born at term after an uncomplicated gestation to a 26-year-old gravida 3, para 2 Arabic woman. Birth weight was 2.28 kg. The father is a first cousin and is 30 years old. Following a breech delivery, the infant required prolonged hospitalization for failure to grow, cleft palate repair, and feeding difficulties. Physical examination showed a length of 56 cm, weight of 5.3 kg, and an OFC of 38 cm with an interpupillary distance of 3.5 cm. The weight was at the 3rd centile

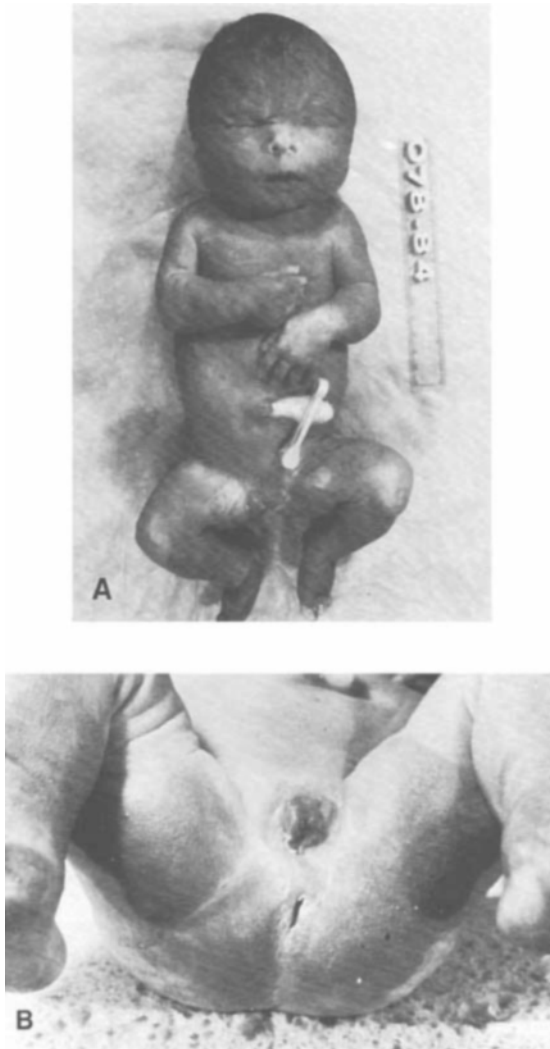


Fig. 2. Frontal view (A) and genitalia (B) of patient 2.

for age 5 months and the other measurements were just below the 3rd centile. There was an unusual head shape (Fig. 3) due to metopic and sagittal suture synostosis and an abnormal facial appearance with hypertrichosis, synophrys, upslanting palpebral fissures, broad nasal root, anteverted nares, downturned corners of the mouth, and anteflexed, malformed ears. There was a repaired cleft soft palate and bilateral anterior ear dimples. Results of specialty evaluations for eye or cardiac anomalies were normal. There was a bilateral bridged palmar crease with camptodactyly of all fingers. There was hyperflexia and spasticity of the lower limbs.

Chromosome study (Fig. 4C) showed an extra chromosome containing the short arm and centromere of 14 attached to bands 3q27→3qter as demonstrated by a maternal reciprocal translocation 46,XXt(3;14)(q27;12). Thus the child's chromosome constitution was 47,XX+der(14)(14pter→q12::3q27→qter).

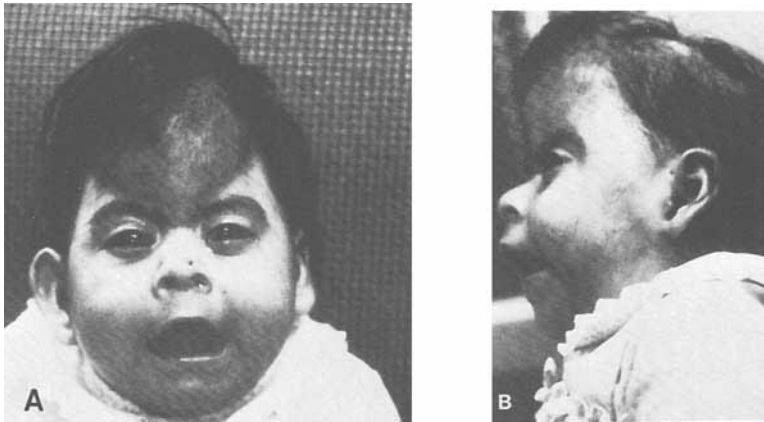


Fig. 3. Frontal and lateral views of patient 3.

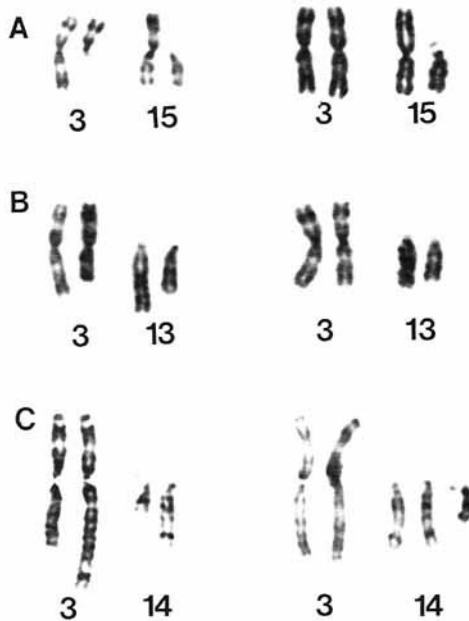


Fig. 4. Partial karyotypes from patients 1-3 and their translocation carrier parents. A, chromosomes 3 and 15 from patient 1 (right) demonstrating duplication of the 3q11→3qter region and deficiency of the 15p11→15pter region due to segregation of a balanced translocation 46,XYt(3; 15)(q11; p11) from the mother (left). B, chromosomes 3 and 13 from patient 2 (right) demonstrating duplication of the 3q25→3qter region and deficiency of the 15q32→15qter region due to segregation of a balanced translocation 46,XYt(3; 13)(q25; q32) from the father (left). C, chromosomes 3 and 14 from patient 3 (right) demonstrating duplication of the 3q27→3qter and 14q12→14qter regions due to 3:1 nondisjunction from a balanced translocation 46,XXt(3; 14)(q27; q12) in the mother (left).

RESULTS AND DISCUSSION

Table 1 summarizes the manifestations of 40 cases of the dup(3q) syndrome as tabulated in the review of Steinbach et al [1981], the single case report of Rosenfeld et al [1981], and the three cases reported here. We have been informed that a dup(3q)

TABLE I. Clinical Manifestations of the dup(3q) Syndrome*

	No.	%
Female sex	23/40	58
Death before 12 months	14/39	36
Hypertrichosis	25/29	86
Abnormal head shape	35/38	92
Upslanting palpebral fissures	15/27	56
Broad nasal root	30/30	100
Anteverted nares	29/32	91
Long upper lip	23/27	85
Maxillary prognathia	18/21	86
Downturned corners of mouth	18/22	82
Highly arched palate	22/22	100
Cleft palate	18/25	79
Malformed auricles	29/31	94
Short or webbed neck	26/28	93
Abnormal chest	23/26	89
Cardiac defects	23/31	75
Omphalocele	3/13	23
Renal or urinary tract anomalies	11/23	48
Genital abnormalities	17/28	61
Clinodactyly	27/30	90
Hypoplastic nails	9/14	64
Simian crease	17/23	74
Talipes	14/22	64
Other skeletal anomalies	17/26	66
Brain anomalies/seizures	19/23	83

*Modified from the table of Steinbach et al [1981], including the case of Rosenfeld et al [1981], the present three cases, and eliminating the case report duplicated in the papers of Boué et al [1974] and Hirschhorn et al [1973].

patient reported by Hirschhorn et al [1973] was inadvertently included in the paper of Boué et al [1974] and therefore counted twice in the summary by Steinbach et al [1981]—Table I corrects for this redundancy. The face of dup(3q) syndrome is quite distinctive and includes hypertrichosis, synophrys, broad nasal root, anteverted nares, downturned corners of the mouth with a long upper lip, malformed ears, and a prominent maxilla. Craniosynostosis is common, as is a short neck and a broad chest with the appearance of widely spaced nipples. Hand anomalies include clinodactyly, camptodactyly, simian creases, nail hypoplasia, and may in extreme cases resemble the clenched fist typical of trisomy 18 (Fig. 1C). Severe mental retardation with underlying brain anomalies and seizures, omphalocele, glaucoma, heart and kidney disease, as well as diverse skeletal anomalies including talipes equinovarus cause a severe clinical course, with 15 of 39 patients not surviving infancy. Resemblance to the Brachmann-de Lange syndrome is superficial, as emphasized by Francke and Opitz [1979], and the two syndromes are easily distinguished during infancy. A detailed comparison of the manifestations [Wilson et al, 1978] indicates intrauterine growth retardation, prominent philtrum, proximally placed thumbs, oligodactyly/phocomelia, and syndactyly of toes 2 and 3 to be more frequent in the Brachmann-de Lange syndrome, whereas craniosynostosis, cleft palate, and urinary tract anomalies are more typical of dup(3q).

Most dup(3q) patients have arisen from segregation of parental rearrangements, as indicated by the present three cases derived from translocations between chromosome 3 and D group chromosomes. Of the 40 cases summarized in Table I, 30 derived from parental rearrangements involving a pericentric inversion of chromosome 3 (11 cases) or balanced translocations between chromosomes 3 and 2 (four cases), 13, 15, 21 (two cases each), 5, 9, 12, 14, and 22 (one case each). Duplication of the 3q25→qter region seems sufficient to generate the characteristic face, although a slightly more severe phenotype is generated by complete duplication of 3q (case 1). Concurrent deleted or duplicated chromosome regions arising from parental rearrangements in dup(3q) patients, as illustrated by the three cases reported here, seem to have little influence on the characteristic phenotype. The potency of the 3q terminus for dysmorphogenesis is further illustrated by the characteristic face of the dup(3q) case reported by Oorthuys et al [1981], which, because it involved an X;3 translocation and manifestations of the Ullrich-Turner syndrome, was not included in this review.

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