Duplication 17q mosaicism: an infant with features of Ellis-van Creveld syndrome

ANDREA SEROTKIN, JUDITH STAMBERG, AND LEWIS WABER

Division of Human Genetics, Schneider Children's Hospital, Long Island Jewish Medical Center, New Hyde Park, NY 11042, USA.

SUMMARY We describe an infant with multiple dysmorphic features who is mosaic for duplication 17q21·1→qter, owing to a direct tandem duplication. He is the first case with mosaicism for a 17q duplication to be reported. His features are strikingly suggestive of Ellis-van Creveld syndrome.

Duplication 17q is extremely rare and until recently no such cases had been reported. In the past few years about a dozen cases of partial duplication 17q have been described and an identifiable syndrome is beginning to emerge.

We report a child with multiple anomalies who was found to be mosaic for duplication 17q21·1→qter but who lacked some features of this syndrome. Mosaicism for a tandem duplication of any chromosomal region is very unusual. Reasons for this are discussed.

Case report

The proband was the first child of healthy, unrelated parents. He was born at 42 weeks' gestation, after a normal term pregnancy, by caesarean section because of failure to progress. At the child's birth the father was 27 and the mother 26 years old. One previous pregnancy had resulted in a miscarriage at 12 weeks. The patient's birth weight and length were on the 25th centile and head circumference was on the 50th centile. He was referred for cytogenetic studies because of brachyrimelia of the extremities, micrognathia, bilateral simian creases, and generalised hypotonia. He had frontal bossing, bilateral ear pits, bilateral polydactyly of the feet,

and dysplastic nails. Also present were penile chordee, bilateral inguinal hernias, a pectus excavatum, a supernumerary rib (right side), a deep anterior palate, and a lip tie. His gums had scalloped edges and two neonatal teeth were evident. He appeared alert and active. Surgery was performed at two months for correction of the chordee and the hernias. At this time the supernumerary toes were removed and circumcision was also performed. At seven months of age a developmental assessment revealed delay in all areas. Cognitive skills were at the five month level and gross motor skills were at the two to three month level. Slow growth was apparent, with both length and weight well below the 5th centile. At one year growth parameters were on the 50th centile for five months for height and three months for weight.

FIGURE G banded partial karyotype from two cells of proband, showing chromosome 17 with the duplication (left) and normal chromosome 17 (right). Arrows indicate duplicated segment q21·1→qter attached to terminus.

Case reports

CYTOGENETIC STUDIES

Chromosome analysis was performed on peripheral blood lymphocytes and on fibroblast cultures established from foreskin and a supernumerary toe. Standard cytogenetic techniques were used including trypsin-Giemsa banding. Analysis of the blood revealed extra chromosomal material attached to the terminus of one chromosome 17 in 36 of 70 cells examined (50%). The remaining cells had a normal male karyotype. The extra segment was identified as a tandem direct duplication of the distal two-thirds of the long arm of chromosome 17 (figure). The karyotype is described as 46,XY/46,XY,dir dup(17)(pter→q25:::q21.1→qter). The foreskin cultures showed the abnormal chromosome 17 in all 54 cells analysed. Cells from a culture established from one of the supernumerary toes showed a mosaic pattern, with 60 of 92 cells abnormal (67%). The parents were not willing to have their chromosomes studied.

Discussion

Duplications of 17q are extremely rare. This is only the thirteenth reported case. Nine of these were the result of a parental translocation inherited in unbalanced form and only four were apparently the result of a de novo event. Naccache *et al*¹ and Bridge *et al*² have summarised the clinical features in patients with duplication distal 17q. A distinct clinical syndrome has been proposed in which the major features are: profound mental retardation, dwarfism or severe growth retardation, psychomotor delay, frontal bossing and temporal retraction, microcephaly, large mouth with thin lips and downturned corners, cleft or highly arched palate, micrognathia, low set malformed ears, short and/or webbed neck, rhizomelia of the extremities, and polydactyly. The region 17q23→qter appears to be the segment correlated with this syndrome.¹

Our patient, who is mosaic for duplication 17q21.1→qter, has a phenotype largely consistent with this picture, although the conspicuous craniofacial dysmorphism is absent. This is surprising considering that our patient has the segment thought to be critical, plus additional duplicated material. Indeed, his duplication corresponds to that of the patient of Gallien *et al*³ whose manifestations were so severe that she died immediately after birth. It may be that the abnormalities in our patient are less severe due to the absence of any monosomy and to the mitigating effect of the normal cell line.

We note that our patient is only the fourth in whom the phenotypic effect of a duplication for part of 17q is not complicated by the effect of monosomy for part of another chromosome. Orye and van Bever⁴ reported a patient who, like ours, had partial

trisomy 17 owing to a de novo tandem duplication. The patients reported by Fryns *et al*⁵ and Parcheta *et al*⁶ had partial trisomy 17 resulting from apparently de novo translocations involving the short arms of chromosomes 21 and 14, respectively. Since the short arms of these chromosomes are polymorphic regions where variability in size or total absence has no effect on the phenotype,⁷ the characteristics of these patients are also attributable purely to the duplication of part of chromosome 17. The lack of a consistent phenotype may be due to the different regions of chromosome 17 included in these duplications. Furthermore, identification of additional material on a chromosome by cytogenetic techniques alone is often difficult when the extra material cannot be traced to a parental balanced translocation. The smaller the length of extra material, the more difficult becomes the problem of identification. In cases where the segment is large, and extended banding techniques are applied, the identification of the segment as a part of chromosome 17 is more reliable.

Our patient's phenotype showed a remarkable resemblance to Ellis-van Creveld syndrome, although there is no consanguinity, no family history of that disorder, and the family is not of Amish descent. Rhizomelic limbs, bilateral polydactyly, dysplastic nails, and natal teeth are frequently encountered in Ellis-van Creveld patients, although in that disorder polydactyly of the hands is more common than polydactyly of the feet. Also not consistent with Ellis-van Creveld syndrome is developmental delay. However, chromosome study may prove useful in other apparently atypical cases of Ellis-van Creveld syndrome.

Our patient represents the first reported case of mosaicism for a duplication involving chromosome 17, and only the sixth reported case of mosaicism for a tandem duplication of any chromosome.⁸ This implies that duplications are more likely to occur as errors in meiosis than in mitosis. Inverted duplications can arise as the result of crossing over within an inversion loop at meiosis in a paracentric inversion heterozygote.⁹ Other mechanisms involving errors at crossing over have also been suggested.¹⁰ It has been speculated that direct duplications can arise as the result of unequal crossing over.^{11 12} Because both types of duplications arise through crossing over, which occurs regularly at meiosis but rarely at mitosis, it is therefore not surprising that mosaic duplications are so rare.

References

- 1 Naccache NF, Vianna-Morgante AM, Richieri-Costa A. Duplication of distal 17q: report of an observation. *Am J Med Genet* 1984;17:633-9.

- ² Bridge J, Sanger W, Mosher G, *et al.* Partial duplication of distal 17q. *Am J Med Genet* 1985;22:229–35.
- ³ Gallien JU, Neu RL, Wynn RJ, Steinberg-Warren N, Bannerman RM. An infant with duplication of 17q21→17qter. *Am J Med Genet* 1981;8:111–5.
- ⁴ Orye E, Van Bever H. De novo distal trisomy 17q. *Ann Genet (Paris)* 1985;28:61–2.
- ⁵ Fryns JP, Parloir C, Van den Berghe H. Partial trisomy 17q. Karyotype 46.XY,der[21],t[17:21][q22:p13]. *Hum Genet* 1979;49:361–4.
- ⁶ Parcheta B, Skawinski W, Wisniewski L, Piontek E, Gutkowska A, Wermenski K. A new case of partial trisomy of 17 long arm. Densitometric analysis of aberrations. *Eur J Pediatr* 1985;143:314–6.
- ⁷ Therman E. *Human chromosomes*. New York: Springer-Verlag, 1986:211–3.
- ⁸ Schwartz S, Schwartz MF, Panny SR, Peterson CJ, Waters E, Cohen MM. Inherited X-chromosome inverted tandem duplication in a male traced to a grandparental mitotic error. *Am J Hum Genet* 1986;38:741–50.
- ⁹ Mules EH, Stamberg J. Reproductive outcomes of paracentric inversion carriers: report of a liveborn dicentric recombinant and literature review. *Hum Genet* 1984;67:126–31.
- ¹⁰ Taylor KM, Franke U, Brown MG, George DL, Kaufhold M. Inverted tandem [“mirror”] duplications in human chromosomes: inv dup 8p, 4q, 22q. *Am J Med Genet* 1977;1:3–19.
- ¹¹ Vogel W, Back E, Imm W. Serial duplication of 10[q11→q22] in a patient with minor congenital malformations. *Clin Genet* 1978;13:159–63.
- ¹² Van Dyke DL, Miller MJ, Weiss L. The origin of inverted tandem duplications, and phenotypic effects of tandem duplication of the X-chromosome long arm. *Am J Med Genet* 1983;15:441–50.

Correspondence and requests for reprints to Dr J Stamberg, Division of Human Genetics, Schneider Children's Hospital, Long Island Jewish Medical Center, New Hyde Park, NY 11042, USA.

De novo partial trisomy 15q (proximal type)

T J HERWEIJER*, J W E OORTHUYS*†, AND N J LESCHOT†

*Department of Pediatrics, and †Department of Human Genetics, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

SUMMARY This report describes a retarded girl with strabismus, high arched palate, antimongoloid slant, low set ears, hearing loss, micrognathia, short neck, and an anteriorly displaced anus. She was found to have a de novo partial trisomy of the proximal part of the long arm of chromosome 15.

De novo partial trisomy of the proximal part of the long arm of chromosome 15 has been described in nine patients.^{1–8} We present the clinical and cytogenetic findings in an infant with partial trisomy of the proximal part of the long arm of chromosome 15.

Case report

The proband was the first child of healthy young parents. Delivery was induced at 42 weeks after a normal pregnancy. Birth weight was 2800 g and length 47 cm. Directly after birth the child showed typical dysmorphic signs, such as a broad nose with a bifid tip, narrow nostrils, telecanthus, blepharophimosis, bilateral absence of the middle phalanx of the fifth finger, abnormal palmar creases, and an anteriorly displaced anus. Respiratory distress

required oxygen and extra suction of the respiratory tract. Respiration was impaired and a nasal stridor was present. A blood sample was taken for chromosome analysis. She was discharged at the age of two weeks.

In the first months frequent upper respiratory tract infections caused adenohypertrophy. In spite of adenotomy, the girl was admitted to hospital several times elsewhere because of decompensation of the heart. At the age of eight months she was seen by a cardiologist and echocardiography revealed right ventricular hypertrophy but no primary cardiac abnormality. The right ventricular hypertrophy was thought to be caused by recurrent respiratory tract infections.

These infections and the narrow nostrils, as well as tube feeding, contributed to upper airway obstruction.

At the age of 15 months she was admitted to our hospital for another adenotomy and uvulectomy. Examination showed a cyanotic, dyspnoeic infant with impaired inspiration. Length was 68 cm (below the 3rd centile), weight 6590 g, and head circumference 45 cm (15th centile). The head was symmetrical. In addition to the findings at birth (telecanthus and blepharophimosis), the eyes showed strabismus convergens, bilateral ptosis, slight antimongoloid slant, and inverse epicanthus (fig 1). There was hypoplasia of the peripheral frontal part

Received for publication 23 March 1987.

Revised version accepted for publication 1 April 1987.