De novo 1;10 balanced translocation in an infant with thanatophoric dysplasia: a clue to the locus of the candidate gene

J H Hersh, F F Yen, S C Peiper, M J Barch, O A Yacoub, D H Voss, J L Roberts

Abstract

A female infant with thanatophoric dysplasia was found to have a de novo translocation involving chromosomes 1 and 10. The chromosome abnormality may represent an important clue in identifying the locus for the candidate gene responsible for this lethal skeletal dysplasia.

(J Med Genet 1995;32:293-295)

Thanatophoric dysplasia (TD) is the most common lethal skeletal dysplasia with a livebirth prevalence estimated to be between 0.28 and 0.6/10 000.^{1,2} Clinically affected infants have marked limb shortening and a small thorax, and death usually occurs in the neonatal period as a result of pulmonary hypoplasia. However, survival into childhood occurs rarely.³ Two forms of TD are felt to exist.⁴ In type 1, there are curved, long tubular bones, especially the femora, very flat vertebral bodies, and usually no evidence of a cloverleaf skull. In type 2, the femora are straight, platyspondyly is milder, and a cloverleaf skull is usually present.

Histopathologically, the growth plate in TD is interrupted by tufts of ossifying tissue, exhibiting features of both endochondral and membranous ossification.⁵

TD is thought to be transmitted in an autosomal dominant fashion.⁵ Since most cases of TD are sporadic, its occurrence in an infant is presumed to be the result of a new autosomal dominant mutation.⁶ We report the first case of TD in which an apparent de novo balanced reciprocal translocation was present in the affected infant.

Case report

A white female, who was the second of twins, was born at 36 weeks' gestation to a 29 year old G2P1 woman and her 36 year old husband. Both had normal stature and there was no consanguinity. In the second trimester, on ultrasound, severe limb shortening, a small thorax, and polyhydramnios were detected in one fetus, with no abnormalities noted in the other fetus. After caesarean section, the infant had marked limb shortening, a small thorax, brachydactyly, macrocephaly without a clover-

Child Evaluation Center, Departments of Pediatrics and Obstetrics and Gynecology, University of Louisville, Suite 500, 224 E Broadway, Louisville, Kentucky 40202, USA
J H Hersh
F F Yen
S C Peiper
M J Barch
O A Yacoub
D H Voss
J L Roberts

Correspondence to: Dr Hersh.

Received 24 August 1994
Revised version accepted for publication 23 November 1994

Figure 1 Whole body radiograph (A) and lateral spine radiograph (B) of the proband. Note the small thorax with horizontal ribs, short long bones with bowed femora and humeri, small iliac bones, horizontal acetabular roofs, small sacroiliac notches, and marked flattening of the vertebral bodies.

Figure 2 Metaphase spread, idiogram, and G banded karyotype showing a reciprocal translocation involving one of the chromosomes 1 and 10 from the proband. Arrows indicate the breakpoints.

leaf skull, and a flat nasal bridge. Length was 34.5 cm (<10th centile), weight 2480 g (>25th centile, <50th centile), and occipitofrontal circumference 36 cm (>90th centile). Radiographic findings were compatible with a diagnosis of TD type 1 (fig 1), including short horizontal ribs and a small thorax, short long bones with bowing and "French telephone receiver" appearance of the femora, small iliac bones, horizontal acetabular roofs, small sacroiliac notches, marked flattening of the vertebral bodies, a large calvarium with short, narrow skull base, absent cloverleaf skull, and extreme shortening and broad appearance of the tubular bones of the hands and feet. The infant died on the second day of life from respiratory failure.

G banded chromosome analysis on blood showed an apparent balanced reciprocal translocation involving one of the chromosomes 1 and 10: 46,XX,t(1;10)(1pter→1q42::10q11.2→10qter;10pter→10q11.2::1q42→1qter) (fig 2). Parental karyotypes were normal. The infant's female twin sib had normal growth parameters and appearance. Examination of the placenta showed that it was diamniotic, dichorionic. Molecular genetic analysis of both placental samples and also of splenic tissue from the affected infant using the microsatellite probe for the apolipoprotein A-II gene on chromosome 1q confirmed dizygosity.

Discussion

Most cases of TD are sporadic.⁶ Autosomal dominant inheritance is supported by the presence of affected monozygotic twins,^{6,7-9} and triplets,¹⁰ presumably resulting from a new autosomal dominant mutation, absence of parental consanguinity, possible paternal age effect, and high new mutation rate.⁶ The finding of TD with cloverleaf skull in sibs who were the products of normal, non-consanguineous parents¹¹ probably reflects germline mosaicism rather than autosomal recessive inheritance.

To date, the genes responsible for TD type 1 and TD type 2 have not been mapped. We speculate that the presence of a de novo chromosomal rearrangement in our case may represent an important clue in identifying the locus for the candidate gene responsible for TD type 1. An increased risk for mental retardation and congenital anomalies is known to be directly related to the presence of a de novo balanced structural rearrangement.¹² This association is thought to develop as a result of a number of different mechanisms. These include the presence of an unbalanced translocation not detected cytogenetically, no loss of chromosomal material, but the translocation breakpoint occurs within the gene, leading to abnormal or absent gene function, or, finally, no chromosomal loss, but a new arrangement of genetic material leading to abnormal gene function.¹² The presence of an apparent balanced, reciprocal translocation in a patient with a known genetic disorder has proven to be valuable in the localisation of the disease gene in a number of conditions, for example, Duchenne muscular dystrophy.¹² In the case of our patient, the chromosomal rearrangement also appeared to be balanced. Therefore, we speculate that the translocation resulted in a gene mutation associated with an alteration or loss of gene function leading to an abnormal phenotype. However, we have been unable to find a relationship between the genes currently mapped to both regions of the chromosomal translocation breakpoints discovered in our patient and the pathogenesis of this skeletal dysplasia.

Chromosomal translocations provide a critical entry point for discovering the gene locus of a genetic disorder by using positional cloning methods. The chromosomal abnormality in our patient is the first to be described in TD. This finding, therefore, may represent the initial step in identifying the gene responsible for this condition, and providing information to determine whether TD type 1 and TD type 2 are genetically distinct entities, with overlapping features.

The authors thank Carolyn Goatley for her assistance.

- 1 Maroteaux P, Lamy M, Robert JM. Le nanisme thanatophore. *Presse Med* 1967;75:2519-24.
- 2 Stoll C, Dott B, Roth MP, Alembik Y. Birth prevalence rates of skeletal dysplasias. *Clin Genet* 1989;35:88-92.
- 3 MacDonald IM, Hutner AGW, MacLeod PM, MacMurray SB. Growth and development in thanatophoric dysplasia. *Am J Med Genet* 1989;33:508-12.
- 4 Langer LO Jr, Yang SS, Hall JG, et al. Thanatophoric dysplasia and cloverleaf skull. *Am J Med Genet Suppl* 1987; 3:167-79.

- 5 Horton WA, Hood OJ, Machado MA, Ahmed S, Griffey ES. Abnormal ossification in thanatophoric dysplasia. *Bone* 1988;9:53–61.
- 6 Corsello G, Maresi E, Rossi C, Giuffre L, Cittadini E. Thanatophoric dysplasia in monozygotic twins discordant for cloverleaf skull: prenatal diagnosis, clinical and pathological findings. *Am J Med Genet* 1992;42:122–6.
- 7 Horton WA, Harris DJ, Collins DL. Discordance for Kleeblatschadel anomaly in monozygotic twins with thanatophoric dysplasia. *Am J Med Genet* 1983;15:97–101.
- 8 Serville F, Carles D, Maroteaux P. Thanatophoric dysplasia of identical twins. *Am J Med Genet* 1984;17:703–6.
- 9 Young ID, Patel L, Lamont AC. Thanatophoric dysplasia in identical twins. *J Med Genet* 1989;26:276–9.
- 10 Sabry A. Thanatophoric dwarfism in triplets. *Lancet* 1974;ii:533.
- 11 Partington MW, Gonzales-Crussi F, Khakes SG, Wollin DG. Cloverleaf skull and thanatophoric dwarfism. Report of four cases, two in the same sibship. *Arch Dis Child* 1971;46:656–64.
- 12 Warburton D. De novo balanced chromosomal rearrangements and extra marker chromosomes identified at prenatal diagnosis: clinical significance and distribution of breakpoints. *Am J Hum Genet* 1991;49:995–1013.