Intrachromosomal triplication of distal 7p

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Abstract

A female infant who died at 2 years of age with growth and psychomotor retardation, wide anterior fontanelle, downward slanting palpebral fissures, large, simple ears, joint dislocation/contractures, recurrent infections, and severe pulmonary hypertension was found to have a *de novo* 7p+ chromosome. The G banding pattern was suggestive of a triplication of 7p21.3 and 7p22; results of fluorescence in situ hybridisation studies using a chromosome 7 specific library, a subtelomeric 7p repeat (109A6), and yeast artificial chromosome clones 786g1 and 850a1, which are respectively associated with the (CA)*n* repeat markers D7S517 and D7S513, supported the cytogenetic interpretation and showed that the middle repeat was inverted. The patient's phenotype was consistent with the 7p duplication syndrome, allowing for the effects of the extra burden introduced by the partial tetrasomy. The present rearrangement may have resulted from several meiotic events occurring at the four chromatid stage, namely an unequal crossover or interhomologue translocation with points of exchange at 7p22 and 7p15 followed by the inverted insertion of 7p21.3→p21.2 at the former breakpoint junction; moreover, a further duplication including D7S517

within the terminal 7p22 band is also required.

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Intrachromosomal triplications have so far been described for 15q11-q13,¹⁻⁵ 9p22-pter,⁶ 5p14-p15.3,⁷ and 2q37.⁸ We report here on a girl with a 7p duplication phenotype resulting from a 7p distal triplication characterised by banding and fluorescence in situ hybridisation (FISH) studies.

Case report

The proband (fig 1) was the fourth child of unrelated parents; at her birth, the mother was 27 and the father 30 years old. The family history was unremarkable and all three sibs were healthy. The pregnancy was uneventful and vertex delivery occurred at 40 weeks. Birth weight was 2500 g; Apgar scores were 7 and 9 at one and five minutes respectively. The post-natal course was characterised by respiratory infections, delayed milestones, and failure to thrive. At 3 months of age her length was 55 cm, weight 2350 g, and OFC 34.5 cm (all below the 3rd centile). She exhibited hypotonia, no head control, widely open anterior

Figure 1 The patient at 7 months of age. (Photograph reproduced with permission.)

Figure 2 Chromosome 7 pairs from three G banded cells of the patient. Note that the rearranged chromosome (on the right in each pair) has two light and two dark extra bands beyond 7p22 and seemingly ends at 7pter.

Figure 3 (A) Result of FISH with the YAC clone 786g1 (D7S517) detected with rhodamine conjugated antidioxigenin (red signals). This clone maps within 7p22. The 7 centromere probe pLC11A (D7Z1), directly labelled with FITC, identifies the 7 homologues. The abnormal 7 (lower) shows three copies of the YAC clone 786g1 signal, one proximal and two distal. (B) Result of FISH with the YAC clone 850a1 (D7S513) detected with rhodamine conjugated antidioxigenin (red signals). This clone maps within distal 7p21. The abnormal 7 on the right of the cell also shows three copies of the signal but in contrast to (A) there are two proximal and one distal signal. The pattern of signals with these two probes strongly suggests that the middle repeat within the triplicated segment is inverted.

dactly. One month later, she died from congestive heart failure.

CYTOGENETIC AND FISH STUDIES

The karyotype of the patient and her parents was assessed on GTG banded metaphases from blood lymphocyte cultures. FISH studies in the proband were performed using a biotinylated chromosome 7 specific library (Cambio, Cambridge), a subtelomeric 7p repeat (109A6),⁹ and YAC clones 786g1 and 850a1, which are associated with the genetic markers D7S517 and D7S513 within bands 7p22 and distal 7p21, respectively.¹⁰ In addition, the 7 centromere probe pLC11A (D7Z1) was used to assist in the identification of the abnormal chromosome. Following in situ hybridisation and stringent washes, 10 metaphases were scored using epifluorescent microscopy, and images were captured and stored with a cooled CCD camera using Smartcapture software developed by Digital Scientific, Cambridge.

The patient had a 7p+ chromosome whereas parental karyotypes were normal. The extra segment, which appeared to be beyond 7p22, consisted of two dark and two light G bands and seemingly ended at 7pter. The extra dark bands were considered to be repeats of 7p21; however, the proximal band was thinner than the distal one so that the former was thought to be only 7p21.3. In contrast, both extra light bands were of similar size (fig 2). The FISH results showed that the 7p+ consisted entirely of chromosome 7 sequences, had a single subtelomeric signal (images not shown), and exhibited three distinct signals for each of the previously mentioned YACs. However, there were one proximal and two distal signals for YAC clone 786g1 but one distal and two proximal copies of the DNA segment identified by the YAC clone 850a1 (fig 3). Overall, there appeared to be a complex rearrangement implying triplication of 7p21.3→p21.2 (D7S513), with the middle repeat apparently inverted in orientation, and for D7S517 in 7p22, and duplication of 7p15, 7p21.1, and most of 7p22 (fig 4). Hence, the rearranged chromosome can be described as 7qter→p22::p21.3→p21.2::p15→p22::p22→pter and the patient's karyotype as 46,XX, trp(7) (p21-p22) de novo.ish trp(7)(p22p21)(wcp7+,c109A6+, D7S517+++ , D7S513+++ , D7Z1+). A cell line is not available.

Discussion

The patient's clinical features, namely growth and psychomotor retardation, wide anterior fontanelle, downward slanting palpebral fissures, large, misshapen ears, small mandible, joint dislocation and contractures, abnormal palmar creases, and recurrent infections associated with IgA deficiency, are consistent with the 7p duplication syndrome.¹¹⁻¹⁴

Although most 7p duplications have resulted from translocations,¹²⁻¹⁴ intrachromosomal duplications account for 11 out of 38 rearrangements.^{11 15-24} These intrachromosomal duplications have involved different segments and two of them were mosaic with a normal cell line.^{11 15} The observed clinical phe-

Figure 4 Schematic representation of the triplicated/duplicated 7p+ chromosome. Note the triplication of 7p21.3 (D7S513) with the middle repeat inverted, and of 7p22 (D7S517), as well as the duplication of 7p15, 7p21.1, and most of 7p22.

fontanelle (6 × 4 cm), antimongoloid palpebral fissures, telecanthus, long philtrum, small mandible, large, Mozart-like ears (bulging appearance of the crura anhelicis and the crus helicis, wide concha, and small lobule), bilateral hip dislocation, camptodactyly of fingers 1-3, and a deep distal palmar crease ending in the second interdigital space in both hands. Cardiac auscultation and ultrasonography, as well as renal echography, showed no anatomical defects. Immunological investigations during a five month period showed low concentrations of serum IgA (out of three tests, 77 mg/ml was the maximum value). IgG, IgM, and IgE values, as well as the results of cellular immunity tests (antigens: candidin and varidase), were normal. A new echocardiogram at 21 months documented severe pulmonary hypertension with right ventricular hypertrophy, enlarged pulmonary artery, and tricuspid failure. At 23 months she was still unable to control her head, had no vocabulary, and showed marked growth retardation (length 72 cm, weight 5400 g, and OFC 39 cm), gaping anterior fontanelle, and pronounced campto-

notypes in this subgroup of patients fit well with the 7p duplication syndrome and show a good correlation with the extent of the duplication. Thus, the phenotypic abnormalities were more severe in children with large non-mosaic duplications^{19,22} than in patients with smaller non-mosaic duplications.^{16,18,20,21,23,24} Incidentally, this comparison appears to confirm that the characteristic craniofacial dysmorphism in the 7p duplication syndrome maps at or around 7p21.^{11,13,14} The clinical picture of our patient is consistent with these correlations and suggests that the extra burden introduced by the tetrasomy resulted in the severe phenotypic consequences, therefore conforming to the principles inferred from other partial trisomy/tetrasomy cases.²⁵

Intrachromosomal triplications seem to result from a common mechanism as indicated by the inverted orientation of the middle repeat often found,^{2,3,5-7} as well as the constant maternal derivation when the parental origin has been ascertained.^{1,2,4,5} In the present case, the signal distribution of YAC clone 850a1 suggested that the middle repeat was also inverted. Although the mechanism accounting for the 7p+ chromosome is unknown, it appears to be a complex one. The combined cytogenetic and FISH data indicate that the 7p+ chromosome resulted from several meiotic events occurring at the four chromatid stage, namely an unequal crossover or interhomologue translocation with points of exchange at 7p22 and 7p15 followed by the inverted insertion of 7p21.3 at the former breakpoint junction; moreover, a "cryptic" duplication including the DNA segment D7S517 within the terminal 7p22 band is also required (fig 4).

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- 1 Holowinsky S, Black SH, Howard-Peebles PN, et al. Triplication 15q11-13 in two unrelated patients with hypotonia, cognitive delays and visual impairment. *Am J Hum Genet* 1993;53:A125.
- 2 Schinzel AA, Brecevic L, Bernasconi F, et al. Intrachromosomal triplication of 15q11-q13. *J Med Genet* 1994;31:798-803.
- 3 Crawford EC, Lethco BA, Bealer D, Schoer RJ, Clarkson KB, Phelan MC. Interstitial duplication and triplication of 15q11-q13 confirmed by fluorescence in situ hybridization. *Am J Hum Genet* 1995;57:A111.
- 4 Chadwick D, Strasberg PM, Farrell S. Intrachromosomal triplication of proximal 15q. *Am J Hum Genet* 1996;59:A114.
- 5 Long FL, Duckett DP, Billam LJ, Williams DK, Crolla JA. Triplication of 15q11-q13 with inv dup(15) in a female with developmental delay. *J Med Genet* (in press).
- 6 Batanian JR, Chen X, Grange DK. Mosaic isodicentric chromosome 9 with triplication (9p22-pter) and no deletion in an abnormal infant presenting with clinical features of trisomy 9; a new type of isodicentric chromosome formation. *Am J Hum Genet* 1994;55:A98.
- 7 Harrison KJ, Teshima I, Silver M, et al. Partial triplication and duplication of 5p14-p15.3 associated with features of trisomy 5p. *Am J Hum Genet* 1996;59:A119.
- 8 Rauch A, Pfeiffer RA, Trautmann U. Deletion or triplication of the $\alpha 3(VI)$ collagen gene in three patients with 2q37 chromosome aberrations and symptoms of collagen-related disorders. *Clin Genet* 1996;49:279-85.
- 9 National Institutes of Health and Institute of Molecular Medicine Collaboration. A complete set of human telomeric probes and their clinical applications. *Nat Genet* 1996;14:86-9.
- 10 Tsui LC, Donis-Keller H, Grzeschik KH. Report of the second international workshop on human chromosome 7 mapping 1994. *Cytogenet Cell Genet* 1995;71:2-21.
- 11 Cantú JM, Rivas F, Ruiz C, Barajas LO, Moller M, Rivera H. Trisomy 7p due to a mosaic normal/dir dup(7)(p13 p22). Syndrome delineation, critical segment assignment, and a comment on duplications. *Ann Genet* 1985;28:254-7.
- 12 Milunsky JM, Wyandt HE, Milunsky A. Emerging phenotype of duplication (7p): a report of three cases and review of the literature. *Am J Med Genet* 1989;33:364-8.
- 13 Lurie IW, Schwartz MF, Schwartz S, Cohen MM. Trisomy 7p resulting from isochromosome formation and whole-arm translocation. *Am J Med Genet* 1995;55: 62-6.
- 14 Reish O, Berry SA, Dewald G, King RA. Duplication of 7p: further delineation of the phenotype and restriction of the critical region to the distal part of the short arm. *Am J Med Genet* 1996;61:21-5.
- 15 Caspersen T, Hulten M, Lindsten J, Zech L. Chromatid interchange resulting in duplication of the short arm of chromosome number 7 in man. *Ann Genet* 1971;14:143-4.
- 16 Šubrt I, Kozák J, Hníková O. Microdensitometric identification of the pericentric inversion of chromosome no 2 and of duplication of the short arm of chromosome no 7 in a reexamined case. *Hum Hered* 1973;23:331-7.
- 17 Dinno N, Doyle J, Weijskopf B, Yen F. Multiple malformations in an infant with 46,XX,7p+. In: Bergsma D, Lowry RB, eds. *Natural history of specific birth defects. Part C of annual review of birth defects, 1976*. New York: Alan R Liss, 1977:228.
- 18 Rockman-Greenberg C, Ray M, Evans JA, Canning N, Hamerton JL. Homozygous Robertsonian translocation in a fetus with 44 chromosomes. *Hum Genet* 1982;61:181-4.
- 19 Zerres K, Schwanitz G, Gelliseen K, Schroers L, Sohler R. Duplication 7p de novo and literature review. *Ann Genet* 1989;32:225-9.
- 20 Debiec-Rychter M, Overhauser J, Kalusewski B, et al. De novo direct tandem duplication of the short arm of chromosome 7(p21.1-p14.2). *Am J Med Genet* 1990;36: 316-20.
- 21 Kleczkowska A, Decock P, Van den Berghe H, Fryns JP. Borderline intelligence and discrete craniofacial dysmorphism in an adolescent female with partial trisomy 7p due to a de novo tandem duplication 7 (p15.1→p21.3). *Genet Couns* 1994;5:393-7.
- 22 Redha MA, Krishna Murthy DS, Al-Awadi SA, et al. De novo direct duplication 7(p11.3→pter) in an Arab child with MCA/MR syndrome: trisomy 7p a delineated chromosomal syndrome? *Am J Hum Genet* 1995;57:A118.
- 23 Schaefer BG, Novak K, Steele D, et al. Familial inverted duplication 7p. *Am J Med Genet* 1995;56:184-7.
- 24 Franz HBG, Schliephacke M, Niemann G, Mielke G, Backsch C. De novo direct tandem duplication of a small segment of the short arm of chromosome 7 (p21.22→22.1). *Clin Genet* 1996;50:426-9.
- 25 Epstein CJ. *The consequences of chromosomal imbalance. Principles, mechanisms, and models*. Cambridge, MA: Cambridge University Press, 1986:55-61.