Chromosome 3p23 break with ring formation and translocation of displaced 3p23→pter segment to 6pter

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Abstract

An 11 year old boy with short stature, learning difficulties, and no obvious facial anomalies has a ring (3)(p23q29) formed by a break in the short arm at 3p23 and subsequent fusion with 3qter. A second rearrangement involving translocation of the displaced 3p23→pter segment to chromosome 6 at 6pter is non-reciprocal with no obvious loss of distal 6pter material. The involvement of one chromosome in two separate rearrangements is uncommon. The patient's relatively mild phenotype appears to be associated with the "ring syndrome" and ring instability in division rather than from any segmental aneuploidy resulting from the presence of the two rearrangements.

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Of the eight reported cases of ring (3) chromosomes,¹⁻⁸ those where breakpoints have been documented⁴⁻⁸ have involved fusion of terminal bands 3p26 and 3q29 in the formation of the ring. Growth and variable mental retardation with mild dysmorphism were common features. We present here an unusual case of a ring (3)(p23q29) where the displaced distal 3p23→pter short arm segment has been translocated to chromosome 6 at 6pter. Such an involvement of one chromosome in two rearrangements, that is, ring formation and translocation of part of the chromosome elsewhere, is very rare. We are aware of only one other case reported before the advent of banding and also involving chromosome 3, where ring formation occurred but with separated chromosome 3 material translocated to a recipient X chromosome at the distal X short arm.¹

Case report

The patient, an 11 year old boy, was studied because of growth retardation and developmental delay. He is the elder of two children of healthy, unrelated parents with no family history of miscarriages. Maternal and paternal ages at birth were 33 and 43 years, respectively. Delivery was by caesarian section, the mother having failed to progress in labour. His birth weight was 3425 g and he had an Apgar score of 8-9. He had slightly overriding sutures, a small fontanelle, and the ears appeared low set;

the head circumference was 35.5 cm. At this stage, his testes were palpable.

At the age of 10 weeks, his weight had not progressed and his length was below the 3rd centile. It was noted that his testes, particularly the right one, were high in the inguinal canals and his feet were everted. The child failed to thrive and multiple investigations began, all of which proved normal. At 5 years, he was difficult, was late in starting school, and continued to fail to thrive. He was much calmer on entering preschool with improving speech, though his hearing appeared diminished in the right ear. On reassessment, his height at 100 cm was below the 3rd centile and his head circumference and weight were between the 3rd and 10th centiles. He had low set ears, slightly coarse hair, a mild systolic murmur, and a high right testicle which was subsequently brought down surgically. At 6 years, he had mild intellectual delay and was slow in psychomotor coordination and balance. Current examination showed no obvious facial dysmorphism (fig 1); his height at 110.5 cm was below the 3rd centile. He functions at an 8 year level in all areas of development.

Cytogenetics and fluorescence in situ hybridisation (FISH) studies

Chromosome analysis was performed on G banded preparations from blood lymphocytes from the proband and his parents. GTG banding showed a ring chromosome formed not from an intact chromosome 3 but by a break at 3p23 and its subsequent fusion with the long arm end at 3qter. The displaced distal 3p23→

Figure 1 Facial appearance of the proband aged 10. (Photograph reproduced with parental consent.)

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Figure 2 Partial karyotype showing the r(3) and der(6) chromosomes. Arrows denote the breakpoints on the ideograms of chromosomes 3 and 6 on the right.

3pter segment was involved in a non-reciprocal translocation with 6pter (fig 2).

FISH studies using a chromosome 3 painting probe (Cambio) confirmed the ring and the distal short arm end of the der(6) to be derived from chromosome 3 (fig 3A). The "All human" telomeric sequence (TTAGGG)_n probe (Oncor) showed a lack of telomeres in the ring (3), but in the der(6) chromosome telomeric sequences were localised at both

ends and also interstitially at the junction of translocation with 3p23 (fig 3B).

No significant loss of 3qter material was evident from G banding and ring formation could involve fusion of 3p23 and 3qter (that is, 3q29) just proximal to the telomeres. The patient's karyotype is interpreted as 46,XY,r(3)(p23q29),der(6)t(3;6)(p23;p25.3) with both rearrangements involving the same chromosome 3.

Of the 100 metaphases analysed, apart from those with the r(3)(p23q29) (83%), ring instability was shown in the number of metaphases without the ring (11%) and with different forms of the ring (6%). The latter include various large sized dicentric (some interlocking) and tetracentric ring configurations as well as monocentric rings occurring in duplicate. Anaphase bridges from dicentric rings in division were confirmed to originate from r(3) when "painted" with the chromosome 3 probe (fig 3C, D)

Micronuclei as evidence of displaced chromatin were observed in 4% of interphase cells while cultures induced with cytochlasin B, which inhibits cytokinesis, showed a higher rate (16%). All micronuclei were also shown to be derived from ring (3) in exhibiting strong hybridisation signals with the chromosome 3 painting probe (fig 3E). Parental chromosomes were normal. A cell line is not available from the patient.

Figure 3 (A) FISH studies using a chromosome 3 specific library probe showed hybridisation to the ring, the normal chromosome 3, and the distal end of the der(6). (B) Localisation of interstitial telomeric (TTAGGG)_n sequences on the der(6) (arrow) and absence of telomeres in ring (small arrow). (C) Anaphase bridge "painted" with chromosome 3 specific library probe. (D) "Painted" bridge breaking at early telophase. (E) Micronuclei with strong hybridisation signals for chromosome 3 (arrows).

Discussion

The dual presence of a ring chromosome and a translocation in a non-reciprocal form is very rare, particularly when the same chromosome is involved in both rearrangements. Only one other patient, a 2 year old girl, had similar involvement of one chromosome in two rearrangements, ring formation and part translocation of the same chromosome, also chromosome 3, to a recipient chromosome, which in her case was the the X short arm.¹ Since this was reported before banding, there was no indication of the extent of chromosome 3 material translocated to Xpter or the likely loss of Xpter. She had more extensive phenotypic anomalies than our present patient with developmental delay, dwarfism, microcephaly, congenital dislocation of the hips, hirsutism, and umbilical hernia.¹

In contrast to other r(3) cases⁴⁻⁸ reported to involve fusion of terminal p26 and q29 bands, the ring (3) seen here was smaller with fusion of 3p23 to 3q29. Though growth failure and mental retardation were common features of r(3),¹⁻⁸ some earlier reports showed mild dysmorphism, microcephaly, and digital anomalies.²⁻⁴ Wilson *et al.*,⁴ in comparing patients with r(3) and those with partial monosomy 3p, noted similarities like microcephaly, ptosis, epicanthic folds, and dysplastic ears and suggested that monosomy for distal 3p may be critical in producing some of the features of their ring (3) phenotype. There was no deletion of distal 3p in our patient who is the only other case reported with a part chromosome 3 derived ring with the break facilitating the transfer of the distal segment 3p23→3pter identified elsewhere.

FISH studies showed a lack of telomeres in the r(3)(p23q29) in our patient. With the removal of the 3p23→3pter segment and therefore 3pter telomeres by translocation, 3qter telomeres also appeared absent from the resultant ring. It is possible that the breakage at 3qter occurred just proximal to the telomeres, perhaps at the adjacent subtelomeric repeats, without disturbing functional 3q sequences. Our patient's developmental delay is evidence of a relatively mild phenotype when compared to a reported case of terminal 3q deletion which also included the adjacent proximal band 3q28 with the patient manifesting cleft lip and palate, microphthalmia, microdolichocephaly, scanty hair, and cardiac abnormalities.⁹

Findings from FISH analysis confirmed what was evident from G banding, the chromosome 3 nature of the ring without the involvement of another chromosome. The non-reciprocal nature of the rearrangement with chromosome 6 was indicated by the presence of interstitial telomeres at the site of translocation with distal 3p; these represented terminal 6p telomeres. Presumably, the 3p23→3pter displaced segment was able to fuse with 6pter with no loss of 6p telomeres or functional gene sequences, as any partial deletion of 6p would probably have contributed to a more adverse phenotype. Patients with monosomy of distal 6p, particularly 6p23→pter, have been

reported to have severe mental retardation, severe to moderate developmental delay, and dysmorphic features including microcephaly, low set, malformed ears, hyperplastic nares, dental anomalies, and short terminal phalanges.¹⁰

Interestingly, structurally abnormal chromosomes involving true telomeric translocations with interstitial telomeres have been variously described.¹¹⁻¹² Fusions of telomeric and non-telomeric sites have included cases of Prader-Willi syndrome translocations which appeared to predispose to translocation of the segment 15q13→qter to the telomeric ends of various recipient chromosomes without disrupting their telomeres.¹¹⁻¹² In such cases, the remaining centric segment (that is, 15pter→q13) was often lost, though in the present patient, stability of the "sticky" end at 3p23 was maintained by fusion with 3qter to form a ring. Similar ring formation of the remaining centric segment 7pter→q22 (after non-reciprocal distal segment translocation of 7q22→qter with chromosome 6 at 6q25) was seen in a minor clone of cells in a patient monosomic for distal 6q.¹³

Of the three breaks that gave rise to the two rearrangements in the patient, the presumably "non-adverse" interruption of intact telomeres at 6pter and subtelomeric repeats at 3qter would leave the remaining 3p23 break with potential to determine the patient's phenotype. Any adverse effects of a disruption at 3p23 could involve (1) a loss of gene function, (2) deletion/mutation at the breakpoint, or (3) "unmasking of recessive genes" at the breakpoint. Though any one of these factors could be important, it is likely that the patient's relatively mild phenotype and lack of any obvious facial dysmorphism except for growth retardation and mental retardation is indicative of the "ring syndrome".¹⁴

Ring chromosomes are formed by breaks in chromosome arms and their subsequent joining. When ring chromosomes replicate, any sister chromatid exchange would result in dicentric rings and anaphase bridges and, depending on where breaks at these bridges occur, rings of various sizes are formed. The instability arising from the mechanics of ring chromosome behaviour in division can also result in the loss of the ring in some cells. The resultant phenotypic effects associated with such ring behaviour can be fairly non-specific and common to all ring chromosomes; these include mild or minimal dysmorphism, but with developmental delay often involving growth and variable mental retardation. Kosztolanyi¹⁴ recognised the consequences of ring instability in division regardless of the chromosome involved, attributing to such instability the "ring syndrome". Aberrant ring chromosome behaviour in cell division is also apparent in their "lagging" and failure to align onto the mitotic spindle leading to their subsequent extrusion as micronuclei in daughter cells.

Evidence of such micronuclei and anaphase bridges representing r(3)(p23qter) behaviour at mitosis has been shown in the patient. Together with the presence of a der(6) with

interstitial telomeres, this case provides a unique insight into the involvement of a single chromosome in two separate rearrangements and our understanding of unusual chromosome anomalies.

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- 1 Mukerjee D, Burdette WJ. Multiple congenital anomalies associated with a ring 3 chromosome and translocated 3/X chromosome. *Nature* 1966;212:153-5.
- 2 Picciano D, Berlin C, Davenport S, et al. Human ring chromosomes: a report of five cases. *Ann Genet (Paris)* 1972;15:241-7.
- 3 Witkowski R, Ullrich E, Piede U. Ring chromosome 3 in a retarded boy. *Hum Genet* 1978;42:345-8.
- 4 Wilson G, Pooley J, Parker J. The phenotype of ring chromosome 3. *J Med Genet* 1982;19:471-3.
- 5 Katitani M, Takahashi H, Yasuda J, et al. A case of ring chromosome 3, 46,XX,-3,+r(3)(p26q29). *Jpn J Hum Genet* 1984;29:157-62.
- 6 Narahara K, Kikkawa K, Murakami M, et al. Loss of the 3p25.3 band is critical in the manifestation of del(3p) syndrome: karyotype-phenotype correlation in cases with deficiency of the distal portion of the short arm of chromosome 3. *Am J Med Genet* 1990;35:269-73.
- 7 Teyssier M, Piperno D, Charrin C. Chromosome 3 en anneau chez un adulte nain et retardé mental. *Ann Genet (Paris)* 1991;34:33-6.
- 8 McKinley M, Colley A, Sinclair P, et al. De novo ring chromosome 3: a new case with a mild phenotype. *J Med Genet* 1991;28:536-8.
- 9 Alvarez Arratia MC, Rivera H, Moller M, et al. De novo del(3)(q2800). *Ann Genet (Paris)* 1984;27:109-11.
- 10 Jalal SM, Macias VR, Roop H, et al. Two rare cases of 6p partial deletion. *Clin Genet* 1989;36:196-9.
- 11 Park VM, Gustashaw KM, Wathen TM. The presence of interstitial telomeric sequences in constitutional chromosome abnormalities. *Am J Hum Genet* 1992;50:914-23.
- 12 Rossi E, Florida G, Casali M, et al. Types, stability, and phenotypic consequences of chromosome rearrangements leading to interstitial telomeric sequences. *J Med Genet* 1993;30:926-31.
- 13 Stevens CA, Fineman RM, Breg WR, et al. Report of two cases of distal deletion of the long arm of chromosome 6. *Am J Med Genet* 1988;29:807-14.
- 14 Kosztolanyi G. Does "ring syndrome" exist? An analysis of 207 case reports on patients with a ring autosome. *Hum Genet* 1987;75:174-9.