Case Reports

Ring chromosome 13 in an Omani infant boy with mental retardation and multiple congenital anomalies

Poothirikovil Venugopalan, MD, FRCPCH, Ravinder K. Kenue, MSc, PhD.

ABSTRACT

An Omani infant boy with severe physical and psychomotor retardation, facial dysmorphism, and anomalies of the cardiovascular and genito-urinary systems is described. The chromosomal analysis revealed a 46, XY, r (13) (p11;q34) karyotype. The cytogenetic basis of this rare abnormality is outlined and phenotypic features are compared with published reports.

Keywords: Ring chromosome 13, phenotype, karyotype, receding forehead, spasticity, ptosis.

Saudi Med J 2001; Vol. 22 (9): 800-803

Constitutional ring chromosomes are rare and are recognized only in 1/25,000 conceptions.[1] Ring chromosome 13 [r(13)] accounts for about 20% of ring chromosomes that are compatible with life.[2] Whilst the majority of these occur as de novo rearrangements, some are inherited.[3] We describe an Omani infant boy with r(13) and multiple congenital malformations.

Case Report. A 6-month old Omani infant boy presented to us with delayed development, shortness of breath and feeding difficulty. He was the 4th child born at term to consanguineous parents aged 35 and 23 years. His birth weight, length and head circumference were below the 3rd percentile. Previous siblings were all normal. Mother had observed diminished fetal movements during the 3rd trimester of pregnancy. Examination revealed a small child with severe growth retardation. He had facial dysmorphism – severe microcephaly (head circumference 28 cm), receding forehead, low set malformed ears, broad nasal bridge, high arched palate, small left palpebral fissure and micrognathia (Figure 1). He was tachypneic and tachycardic. He had significant cardiomegaly, left parasternal heave, accentuated pulmonary 2nd heart sound and a grade 3/6-pansystolic murmur best audible over the lower left parasternal region. Lungs were clear. Liver was palpable 5 cm below the right costal margin in the midclavicular line, and was soft and tender to palpation. He was spastic with flexion deformities of hip, knee and elbow. Developmental age was below 2 months. Deep tendon reflexes were exaggerated and plantars upgoing. He also had bilateral undescended testes and penile hypospadias. Investigations revealed normal blood counts and coagulation profile, cardiomegaly and increased pulmonary vascularity on chest radiograph, and right axis deviation and biventricular hypertrophy on electrocardiogram. Echo-Doppler studies confirmed a large ventricular septal defect with pulmonary hypertension. Ultrasound scan of the abdomen showed the undescended testes in the inguinal canal. Skeletal survey and Computerized Tomograms (CT)

From the Departments of Child Health (Venugopalan) and Human & Clinical Anatomy (Kenue), Sultan Qaboos University, Muscat, Sultanate of Oman.

Received 23rd December 2000. Accepted for publication in final form 3rd April 2001.

Address correspondence and reprint request to: Dr. P. Venugopalan, Child Ward 2, Sultan Qaboos University Hospital, PO Box 38, PC 123, Sultanate of Oman. Tel. +968 513562. Fax. +968 513009. E-mail: gopalax@omantel.net.om

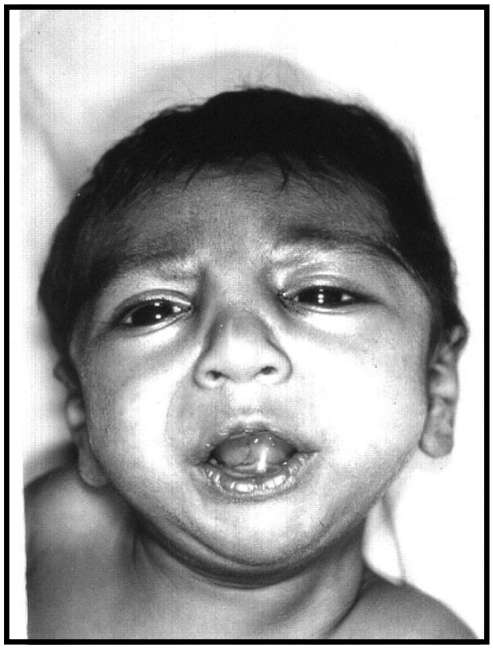

Figure 1 - Photograph of face (close-up) showing facial dysmorphism.

of the brain did not reveal any abnormality. Chromosome analysis carried out on cultured peripheral blood lymphocytes, using G- and Q-banding techniques, showed 46, XY, r(13) (p11;q34). No mosaicism was observed. Both parents had normal chromosomes. Follow-up repeat chromosome analyses on the patient over the next 3 years established the stable nature of the r(13).

Discussion. ***Clinical features.*** The phenotypic features of ring chromosome 13 [r(13)], first described by Lejeune et al in 1968,[4] are characteristic and include severe psychomotor retardation, dysmorphic facies, central nervous and genitourinary anomalies. In 1992 Brandt et al[5] reviewed 22 patients with r(13) and reported microcephaly, severe mental retardation and multiple malformations. More than one half of the patients also showed growth retardation, facial dysmorphism, abnormal ears, high arched palate, and foot and toe anomalies. Other associations with the syndrome include retinal detachment,[6] limb anomalies, imperforate anus, iris coloboma, and developmental anomalies of the brain,[7] agenesis of corpus callosum, aprosencephaly and ambiguous genitalia.[8-10] More recently celiac disease and keratoconus have been associated with r (13).[11,12] Occasionally the child has only minor clinical features like alopecia, pigmentation, trigonocephaly and telecanthic folds.[13,14] Our patient had many of these manifestations. In addition, he had ptosis of the left eye of congenital origin and bilateral undescended testes. He also had cardiovascular anomalies (ventricular septal defect and patent ductus arteriosus) which are relatively uncommon in this syndrome. The observation of decreased fetal movements noted in our patient has not been described in any of the published reports. Our patient showed a receding forehead and spasticity unlike the protruding forehead and hypotonia commonly associated with the syndrome. He also did not show any abnormalities on CT scan of brain or on skeletal survey.

Cytogenetics. Ring chromosome formation in the majority of cases has been attributed to breaks in both arms of the chromosome and fusion of the exposed tips of the chromosomes into a circular structure.[3] The segments distal to the breakpoints are therefore lost, giving rise to a partial monosomy for the distal short arm and distal long arm. This generally leads to major dysmorphogenesis and mental retardation. Larger deletions of 13q are more likely to cause a severe clinical syndrome than smaller deletions and anencephaly has been reported in a patient with deletion of the segment 13q32-qter in a r(13).[15] Generally ring chromosomes are associated with a more severe phenotype than corresponding simple deletions.[3] This could be attributed to the involvement of gene rich regions adjacent to telomere (subtelomeric sequences) in ring chromosomes unlike simple deletions.[16] Our patient had the break point at 13q34, the band frequently deleted in r(13) cases, which contains many functionally important genes for example Collagen IV alpha 1, Collagen IV alpha 2 polypeptide (COL 4A1 and COL 4A2), Coagulation factor VII and X (F 7 and F10), Inhibitor of Growth 1 (ING 1) and Lysosomal associated membrane protein 1 (LAMP 1).[17-20] The loss of these could be an explanation for the multisystem involvement in r(13). Some rings show instability at cell division.[3] The consequences of rings becoming entangled, broken, doubled or otherwise disrupted (due to sister chromatid exchange) during cell division are immense. In these either the ring chromosome is lost altogether (resulting in monosomy) or products of broken ring such as deleted chromosomes, acentric fragments, or centric fragments or additional rings may occur. Some abnormal cell lines are selected against and die, and provide an alternate explanation for the growth retardation, mental retardation and dysmorphogenesis.[21] The ring chromosomes are also reported with telomere-to-telomere fusion and some patients show interstitial telomeric repeats in their ring chromosomes.[22] Ring chromosome formation in which asymmetric breakage and reunion of the long arm of an intermediate isochromosome or Robertsonian chromosome, forms a large dicentric ring chromosome.[23] Sister chromatid exchange in ring chromosome has been suggested as the origin of rings of various sizes in individuals with ring chromosome mosaicism. Stable ring chromosomes show C-bands and alpha satellite arrays similar to the

corresponding normal chromosome. Size variation is minimal and structural rearrangements at cell division uncommon. The patients with ring chromosome should be monitored for its stability over a period of time.[24] Our patient's ring was stable as ascertained by repeat study in the subsequent years.

Correlation of karyotype with phenotype. Depending on the site of the breakpoint namely, size of the deleted segment, 3 phenotypes of r(13) with considerable overlap have been described.[5] Breakpoint at 13q34/13q33 is associated with mental retardation, microcephaly, craniofacial dysmorphism. Breakpoint at 13q32/13q31 shows in addition absent or hypoplastic thumbs and deletion involving 13q14 predisposes to retinoblastoma. Chromosome 13 is known to harbor tumor suppressor genes and r(13) has been associated with retinoblastoma and rhabdomyosarcoma.[25] Clinical features in our patient correlates with the distal breakpoint, however considerable phenotypic heterogeneity exists even within each sub-group. These additional features should be cautiously attributed to the r(13) and could have been caused by other genetic or environmental factors. Patients with r(13) resulting from telomere to telomere fusion are a special group and show only minimum phenotypic consequences.

Inheritance. The majority of cases of r(13) are sporadic. Mostly parents of affected children are clinically and cytogenetically normal. However, occasionally the condition may be inherited from a parent who is mosaic for r(13)[26] or with isolated germline involvement, and hence phenotypically normal or only minimally abnormal. Both parents of our patient were phenotypically normal and had normal karyotypes.

In conclusion, we have described an Omani infant boy with stable r(13) born to normal parents and associated with severe mental retardation and multiple anomalies. In addition to the commonly described phenotype, he had ptosis of the left eye, bilateral undescended testes, congenital heart disease, receding forehead and spasticity. Also the observation of decreased fetal movements noted in our patient has not been described in any of the published reports. As the spectrum of associations with r(13) is wide, precise breakpoints in the ring chromosome and their known phenotypic consequences should be carefully characterized for each patient.

References

1. Jacobs PA. Mutation rates of structural chromosome rearrangements in man. Am J Hum Genet 1981; 33: 44-54.
2. Bargaonkar DS. Chromosomal variation in man: a catalog of chromosomal variants and anomalies. 8th edn. New York: Wiley-Liss; 1997.
3. Gardner RJM, Sutherland GR. Chromosome abnormalities and genetic counselling. Oxford: Oxford University Press; 1989.
4. Lejeune J, Lafourcade J, Berger R, Cruveiller J, Rethore MO, Dutrillaux B et al. Etude de trois cas de chromosomes D en anneau. Ann Genet (Paris) 1968; 11: 79-87.
5. Brandt CA, Hertz JM, Petersen MB, Vogel F, Noer H, Mikkelsen M. Ring chromosome 13: lack of distinct syndromes based on different breakpoints on 13q. J Med Genet 1992; 29: 704-708.
6. Filous A, Raskova D, Kodet R. Retinal detachment in an infant with the ring chromosome 13 syndrome. Acta Ophthalmol Scand 1998; 76: 739-741.
7. Parcheta B, Wisniewski L, Piontek E, Szymanska J, Skawinski W, Wermenski K. Clinical features in a case with ring chromosome 13. Eur J Pediatr 1985; 144: 409-412.
8. Niebuhr E, Ottosen J. Ring chromosome D(13) associated with multiple congenital malformations. Ann Genet (Paris) 1973; 16: 157-166.
9. Boduroglu K, Alikasifoglu M, Tuncbilek E, Uludogan S. Ring chromosome 13 in an infant with multiple congenital anomalies and penoscrotal transposition. Clin Dysmorphol 1998; 7: 299-301.
10. Goldsmith CL, Tawagi GF, Carpenter BF, Speevak MD, Hunter AG. Mosaic r(13) in an infant with aprosencephaly. Am J Med Genet 1993; 47: 531-533.
11. Heaven CJ, Lalloo F, Mchale E. Keratoconus associated with chromosome 13 ring abnormality. Br J Ophthalmol 2000; 84: 1079.
12. Talvik I, Ounap K, Bartsch O, Ilus T, Uibo O, Talvik T et al. Boy with coeliac disease, malformations, and ring chromosome 13 with deletion 13q32-->qter. Am J Med Genet 2000; 93: 399-402.
13. Fryns JP, Devriendt K, Legius E. Skin pigmentation anomalies in ring chromosome 13. Genet Couns 1998; 9: 155-156.
14. Duckett DP, Porter HJ, Young ID. Trisomy / partial monosomy 13 mosaicism associated with relatively mild clinical malformation. Ann Genet 1992; 35: 113-116.
15. Schmid W, Muhlethaler JP, Briner J, Knechtli H. Ring chromosome 13 in a polymalformed anencephalic. Humangenetik 1975; 27: 63-66.
16. Saccone S, De sario A, Della Valle G, Bernardi G. The highest gene concentrations in the human genomes are in telomeric bands of metaphase chromosomes. Proc Acad Sci USA 1992; 89: 4913-4917.
17. Cutting GR, Kazazian HH Jr, Antonarakis SE, Killen PD, Yamada Y, Francomano CA. Macrorestriction mapping of COL4A1 and COL4A2 collagen genes on human chromosome 13q34. Genomics 1988; 3: 256-263.
18. Kasai R, Narahara K, Namba H, Tsuji K, Matsubara T, Hiramoto K, et al. Mapping of genes encoding coagulation factors VII and X to the distal portion of the 13q34 by gene dose study in a patient with r(13). Jinrui Idengaku Zasshi 1989; 34: 247-250.
19. Mattei MG, Matterson J, Chen JW, Williams MA, Fukuda M. Two human lysosomal membrane glycoproteins, h-lamp-1 and h-lamp-2, are encoded by genes localized to chromosome 13q34 and chromosome Xq24-25, respectively. J Biol Chem 1990; 265: 7548-7551.
20. Zeremski M, Horrigan SK, Grigorian IA, Westbrook CA, Gudkov AV. Localization of the candidate tumor suppressor gene ING1 to human chromosome 13q34. Somat Cell Mol Genet 1997; 23: 233-236.
21. Sigurdardottir S, Goodman BK, Rutberg J, Thomas GH, Jabs EW, Geraghty MT. Clinical, cytogenetic and fluorescence in situ hybridization findings in two cases of "complete ring" syndrome. Am J Med Genet 1999; 87: 384-390.

22. Murtif-Park V, Gustashaw KM, Wathen TM. The presence of interstitial telomeric sequences in constitutional chromosome abnormalities. Am J Hum Genet 1992; 50: 914-923.
23. Stetten G, Tuck-Muller CM, Blakemore KJ, Wong C, Kazazian HH, Antonarakis SE. Evidence for involvement of a Robertsonian translocation 13 chromosome in formation of a ring chromosome 13. Mol Biol Med 1990; 7: 479-484.
24. Geisselsson D, Hoglund M, Mertens F, Johasson B, Dal Cin P, Van den Berghe H et al. The structure and dynamics of ring chromosomes in human neoplastic and non-neoplastic cells. Hum Genet 1999; 104: 315-325.
25. Kapandze B, Kashuba V, Baranova A, Rasool O, van Everdink W, Liu Y et al. A cosmid and cDNA fine physical map of a human chromosome 13q14 region frequently lost in B-cell chronic lymphocytic leukemia and identification of a new putative tumor suppressor gene, Leu5. FEBS Lett 1998; 426: 266-270.
26. Hsu LY, Yu MT, Richkind KE, van Dyke DL, Crandall BF, Saxe DF et al. Incidence and significance of chromosome mosaicism involving an autosomal structural abnormality diagnosed prenatally through amniocentesis: a collaborative study. Prenat Diagn 1996; 16: 1-28.