Mosaic Ring Chromosome 14 and Monosomy 14 Presenting with Growth Retardation, Epilepsy, and Blepharophimosis

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Ring chromosomes are rare chromosomal anomalies and usually not stable in nature. Patients carrying ring chromosome have various phenotypes depending on the degree of structural rearrangement. A 1-year-old boy, presenting with hypotonia, blepharophimosis, ptosis, a bulbous nose, mild psychomotor retardation, and epilepsy, was found to have mosaicism of chromosome ring 14 and monosomy 14. His karyotype is described as hitherto unreported mos 46, XY, r(14)(p11.2q32.31 or q32.2)[84]/45, XY,-14[10]/46, XY, dic r(14)[6]. His seizures responded well to phenobarbital. He has marked growth retardation but less serious delays in mental and motor development than those with ring 14 described in the literature. *(Chang Gung Med J 2004;27:373-8)*

Key words: chromosome 14, ring chromosome 14, monosomy 14, seizure, growth retardation.

Ring chromosomes arise from chromosome breaks occurring on either end of the arms and subsequent rejoining of the broken ends.[1] In ring chromosomes from acrocentric groups, the telomeres or p arm (rRNA) may be lost.[1-3] Ring chromosome 14 is a rare chromosomal aberration associated with a characteristic syndrome, including mental retardation and epilepsy.[4] The ring chromosome usually represents distal monosomy 14q32.3.[4,5] In this study, a child with mosaic ring 14 was reported. The mosaicism, consisting of partial trisomy 14 and monosomy 14, was detected by G-banding, Ag-NOR staining, and fluorescence in situ hybridization (FISH) studies.

CASE REPORT

Our patient, a boy, the second child of young, healthy and non-consanguineous parents, was born via induced vaginal delivery at 35 weeks due to premature rupture of the membranes and fetal distress. There was no history of teratogen exposure during pregnancy. His birth weight was 1600 g, body length 42 cm, and head circumference 27.5 cm (all below the 3rd percentile). After birth this patient suffered from respiratory distress, hyperbilirubinemia and gastric bleeding. Physical examination at 1 year old showed a small baby with brachy-microcephaly, blepharophimosis, ptosis, downward slanting palpebral fissures, epicanthal folds, hypertelorism, depressed nasal bridge with a bulbous nose, thin upper lip (Fig. 1), high-arched palate, and short neck. The anterior fontanel was nearly closed. Brain ultrasonograhy and eye ground examination were normal. A grade II systolic murmur was heard over the left sternal border. Babinski sign was present. A previous echocardiography showed an atrial septal defect (ASD) and a patent ductus arteriosus (PDA). The hearing test was normal. Chromosome study showed 45,XY,-14/46,XY, r(14)(p11.2q32.31 or q32.2)/46,XY, dic r(14)in a ratio of 10/84/6 analyzed in 100 metaphases (Fig. 2A). By using Ag-NOR staining (Fig. 2B) and FISH (Fig. 3), different cell clones, including monosomy for chromosome 14, and a ring

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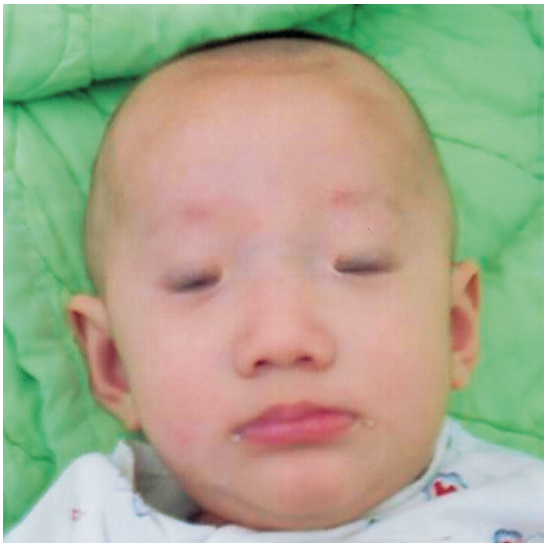
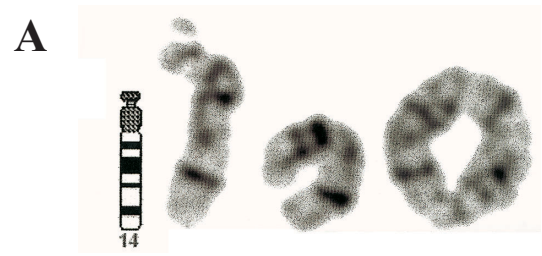


Fig. 1 Patient at 1 year of age.



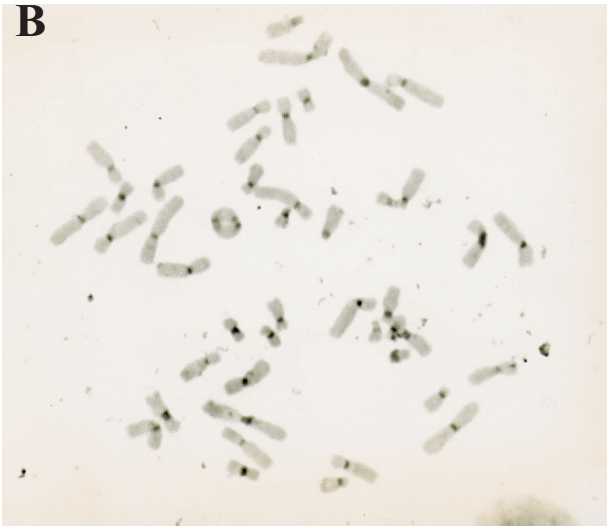
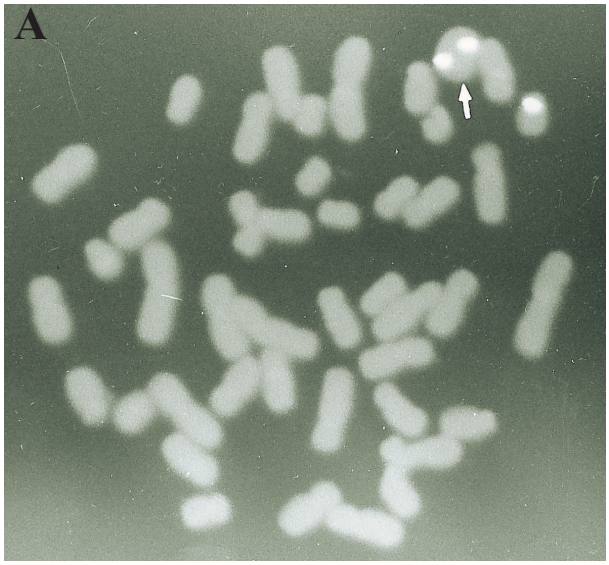


Fig. 2 Partial karyogram revealing ring(14) and dicentric r(14) (A), as shown by AgNOR staining(B).



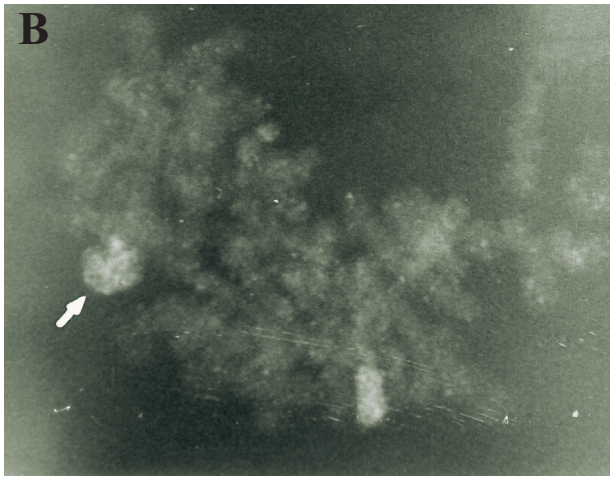


Fig. 3 FISH study by α-satellite (A) and painting probes (B) for chromosome 14 showing double ring form chromosomes.

or dicentric (double) chromosome 14 were demonstrated.

The PDA was ligated and ASD repaired at 10 days and 4 months of age, respectively. Seizures occurred after the age of 7 months. An electroencephalogram showed mildly diffuse cortical dysfunction without abnormal epileptiform discharges. Hemogram, electrolytes, blood glucose and metabolic screening were all normal. The seizures could be controlled by phenobarbital (5 mg/kg/day) and vitamin B6 (50 mg/day). Mild motor delay was noted (head control at 6 months, walking at 15 months). At

the age of 1 year, his growth parameters were still far below the 3rd percentile. He was seizure-free without other complicated problems.

DISCUSSION

A rare case of ring chromosome 14 with a characteristic dysmorphic facies and features, including mental retardation and epilepsy, is described. The clinical presentation of this patient is consistent with, but milder than, reported cases of 14q deletion or rin(14) (Table 1). The patient's karyotype showed a ring chromosome 14 in 100 cells analyzed. Eighty-four showed 46 chromosomes with one ring, 6 showed a double ring, and in 10 cells the ring was missing. The manifestations of ring chromosome 14 contribute to the terminal deletion of the long arm, most probably distal to band 14q32. However, the combination of monosomy (loss of the ring chromosome), terminal deletion in the ring, or partial trisomy in the dicentric ring leads to different phenotypes depending on the composition of different cell clones.[1] In this report, the majority of the cells had a ring(14) with a few cells with monosomy and trisomy 14. This could explain why the cardinal features (growth retardation, blepharophimosis and epilepsy) in this patient were milder than in patients carrying ring(14) syndrome with more monosomic or trisomic chromosome 14 cell lines.[3,4,6,7]

Patients with ring 14 share common clinical

Table 1. Comparison of Proximal Trisomy 14q, Ring 14 and Del(14)(q32.3) Syndromes

Features/Chromosome anomalies	Trisomy 14q (proximal)[13]	Ring 14 (p13q32.3) [6,14]	Del(14)(q32.2)[15]	Present case
Psychomotor retardation	moderate-severe	moderate-severe	moderate (3/5), mild (2/5)	mild
Growth	SGA, postnatal growth failure	feeding difficulty with growth retardation	*low BH (1/5), BW (2/5), and HC (2/5)	SGA, *low BW, BH, and HC
Craniofacial dysmorphism	brachycephaly	high forehead, dolichocephaly	high forehead with lateral hypertrichosis	brachycephaly
Ear	low-set, malformed	low-set, dysplastic	not mentioned	normal
Eye	down-slanting palpebral fissures, microphthalmia/ strabismus, hypo-/ hypertelorism, ptosis	down-slanting palpebral fissures, hypertelorism, ptosis, microphthalmia, abnormal eyeground (some)	ptosis (2/5), esotropia (1/5), optic nerve coloboma (1/5), epicanthal folds	down-slanting palpebral fissures, hypertelorism, epicanthal folds, ptosis, blepharophimosis
Nose	broad base and prominent nasal tip, prominent philtrum	flat nasal bridge, prominent bulbous nasal tip	broad nasal bridge	flat nasal bridge, prominent bulbous nasal tip
Mouth and neck	large, thin upper lip, micrognathia, high-arched palate or cleft, short neck	thin upper lip with down turned corners of mouth, micrognathia, high-arched palate, short and web neck	high-arched palate	thin upper lip, micrognathia, high-arched palate, short neck
Seizure	GTC	GTC or CPS	nil	GTC
Brain anomaly	microcephaly	microcephaly, cerebral atrophy with ventriculomegaly	microcephaly (2/5)	microcephaly
Congenital heart defects	3/9	often	2/5	PDA, ASD
Genito-urinary malformation	2/9 (cryptorchidism)	cryptorchidism	nil	normal
Outcome	variable (not good)	variable (not good), short life span (average: 78 months)	fair	alive and well

Abbrevations: SGA: small for gestational age BH: body height; BW: body weight; HC: head circumference; GTC: generalized tonic-clonic seizure; CPS: complex partial seizures; PDA: patent ductus arteriosus; ASD: atrial septal defect.

manifestations. Clinical features of ring[14] syndromes typically include prenatal and postnatal growth retardation, psychomotor retardation, persistent respiratory infections, and a characteristic facies.[4] Their phenotype has been attributable to the terminal deletion of the long arm, most probably distal to band 14q32,[3] which is rather different from 14q deletion (Table 1).

Seizures are present in almost all cases, usually appearing between 1 month and 4 years of age. This feature is not consistently seen with other ring chromosomes, with the exception of chromosome 20.[1,4] Most of the seizures associated with ring 14 are of the primary generalized types. Seizures seen in r(14) patients could be due, not to the presence of the ring chromosome per se, but to the deletion of a locus in the proterminal region of 14q on one homologue.[5] However, the absence of seizures in some patients with terminal deletions of 14q, and the seizures seen occasionally in patients with other ring chromosomes, have been taken as evidence that the seizure disorder is due to ring chromosome instability.[8,9] Few cases present with complex partial seizures.[6,7] Other neurologic anomalies such as hypoplastic corpus callosum, ventriculomegaly, porencephaly, and focal cerebral atrophy have been reported, indicating a focal disturbance in the CNS.[3-5,7]

Only the D group ring chromosomes (no. 13-15) form dicentric and interlocked rings.[1,2,10] Large ring chromosomes in man are more unstable. They show more variation in size, and are involved in more abnormal mitosis than smaller ones, and thus tend to be lost due to lagging.[2] Mitotic instability of the ring chromosome, resulting in somatic mosaicism with some cells monosomic for chromosome 14, occurs in the peripheral blood of most patients.[4] This mosaicism in cells of the central nervous system, which results in cell death, could account for the seizure phenotype. Ring instability may be markedly different in the peripheral blood than in other tissues.[2,6] A somatic cross-over within the ring may result in a double sized dicentric ring which can break during anaphase. Sister chromatid exchange within a ring chromosome can lead to the formation of a double ring followed by chromosome breakage at anaphase if the centromeres of the dicentric double ring attempt to move to opposite poles. Rejoining of the broken ends of the double ring can result in a ring chromosome with an imbalance of chromosome material.

The breakpoint on q32.2-q32.3 of this ring chromosome thus lies within an interval of approximately 350 kb, within the variable (IGHV) or diversity (IGHVD) regions of the IGH gene cluster.[11] Some important genes, CKB (creatine kinase brain) and Ig (immunoglobulin) heavy chain genes, are located between 14q32 and 14qter, which may be implicated in the manifestation of ring (14).[12] The CKB gene catalyzes the reversible transfer of the phosphate group between creatine and adenosine triphosphate. Two dissociable subunits, of either the muscle (M) or brain (B) type, associate to form MM, MB, or BB dimers. Among them, BB dimers may be related to the clinical expression of ring 14 and the beginning of corpus callosum formation. More detailed molecular analyses are required to determine the characteristic features of ring 14 chromosome.

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以生長遲滯、癲癇、與眼裂狹窄爲表現的環形染色體十四及單體症

侯家瑋

環形染色體是一種罕見的染色體異常，性質上也不穩定。帶有環形染色體的病人常因此染色體重組之構造變化嚴重程度而有變異頗大的表現型。一名一歲男孩因肌肉張力低下、眼裂狹窄、眼瞼下垂、球形鼻、精神運動發展遲緩及抽搐而做染色體檢查。結果發現爲拼湊型第十四號染色體環形及單體症，其核型爲45,XY,-14/46,XY,r(14)(p11.2q23.31或q32.2)/46,XY,dicr(14)(比例爲10/84/6)。此病人之臨床表徵符合環形染色體14之描述。另外，他的第十四號染色體單體症、環形染色體之長臂末端缺損及雙環之部分三體症可解釋此病人之對phenobarbital較佳反應與較輕微之表現型。(長庚醫誌 2004;27:373-8)

關鍵字：第十四號染色體，環形染色體十四，第十四號染色體單體症，抽搐，生長遲緩。

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