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SHORT COMMUNICATION

Case report of de novo dup(18p)/del(18q) and r(18) mosaicism

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Abstract This is a report of a 27-year-old woman with an unusual de novo chromosomal abnormality. Mosaicism was identified in peripheral blood cells examined by standard G-bands by trypsin using Giemsa (GTG) analysis and fluorescence in situ hybridization (FISH) analysis with chromosome-18 region-specific probes, 46,XX,del(18)(pter → q21.33:)[41], 46,XX,r(18)(::p11.21 → q21.33::)[8], and 46,XX,der(18)(pter → q21.33::p11.21 → pter)[1]. On the other hand, the karyotype of periodontal ligament fibroblasts was nonmosaic, 46,XX, der(18)(pter → q21.33::p11.21 → pter)[50]. All cell lines appeared to be missing a portion of 18q (q21.33 → qter). The pattern of the dup(18p)/del(18q) in the rod configuration raises the possibility of an inversion in chromosome 18 in one of the parents. However, no chromosomal anomaly was detected in either parent. The most probable explanation is that de novo rod and ring configurations arose simultaneously from an intrachromosomal exchange. The unique phenotype of this patient, which included primary hypothyroidism and primary hypogonadism, is discussed in relation to her karyotype.

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Introduction

Deletion of the long arm of chromosome 18 [del(18q)] occurs in about 25 of every one million newborns. Del(18q) syndrome is characterized by short stature, microcephaly, disturbed brain myelinization, mental deficiency, hypotonia, midface hypoplasia, prominent anthelix, hearing impairment, tapered fingers, and genital abnormalities, particularly in males (Wertelecki and Gerald 1971; Gorlin et al. 1990; Schinzel et al. 1991; Gay et al. 1997; Cody et al. 1999; Linnankivi et al. 2003). Congenital heart defects may also be found (Gorlin et al. 1990; Sturm et al. 2000). A variety of other features have been recorded, including cleft palate, eye abnormalities, downturned corners of the mouth, low-set ears and a low hair line (Gorlin et al. 1990; Cody et al. 1997; Gustavsson et al. 1999; Zannolli et al. 2003).

Several studies have reported growth hormone deficiency in patients with del(18q) (Cody et al. 1997; Ghidoni et al. 1997; Hale et al. 2000). Ghidoni et al. (1997) suggested that a gene or genes on the long arm of chromosome 18 may be involved in growth hormone production. Hypothyroidism and hypogonadism occur less commonly. Pernicious anemia, ectodermal dysplasia, harlequin ichthyosis, autoimmune thyroiditis, and insulin-dependent diabetes mellitus also have been reported, albeit rarely (Dacou-Voutetakis et al. 1999; Gustavsson et al. 1999; Stewart et al. 2001; Zannolli et al. 2003). Immunoglobulin A (IgA) deficiency has been recorded in several instances (Hecht 1969). The clinical spectrum varies greatly depending on the extent of the deletion. Terminal deletions

of the long arm of chromosome 18 are most common, and in some cases, the deletion occurs from one or both arms of chromosome 18, and the chromosomal ends join to form a ring (Stankiewicz et al. 2001). Most patients with r(18) are female, usually have a less severe phenotype than found with del(18q) (Miller et al. 2003), and may be associated with a short neck without cardiac anomalies (Stankiewicz et al. 2001). Patients may sometimes show mosaicism with more than one chromosomal anomaly, such as the combination of del(18q) and r(18).

On the other hand, rod/ring mosaicism, in which the rod and ring configurations arise simultaneously, has been reported in chromosome 2 (Wyandt et al. 1982). We describe herein an unusual case of de novo rod/ring mosaicism, dup(18p)/del(18q), and r(18), with primary hypothyroidism and primary hypogonadism.

Case report

The patient was a 27-year-old Japanese woman with a chief complaint of malocclusion and articulation problems. The patient was the first child of nonconsanguineous, healthy parents. At the time of her birth, her mother and father were both 25 years old. The patient was born at 41 weeks gestation with a birth weight of 2,555 g and length of 48 cm. She was found to have a cleft lip and palate. No chromosomal anomaly was detected in either her parents or brother. The medical history of this patient included lip closure at 6 months, hard-palate closure at 1 year 6 months, fistula closure at 2 years 9 months, surgery for foot deformity at 3 years, pharyngeal flap surgery at 7 years, and secondary bone grafting for cleft site at 23 years. From age 6–17 years, the patient had speech therapy. Since age 17, she has received hormone replacement therapy (l-thyroxine and estrogens) for primary hypothyroidism due to Hashimoto thyroiditis and amenorrhea due to primary hypogonadism, respectively. We obtained permission from the patient and her parents for publication.

General examination

The phenotype of this patient was mostly consistent with del(18q) syndrome, including mental retardation, short stature, and hypotonia. An examination revealed several skeletal abnormalities. She had short, thin, and tapered fingers, proximally placed thumbs, clinodactyly, feet deformity (Fig. 1), vertebral fusion (C2–C3) (Fig. 2a, b), short neck, and enlarged elbow joints. Ectodermal dysplasia of the skin, hair, and nails was also observed. The patient was found to have decreased secondary sexual characteristics, including undeveloped breasts and sparse axillary and pubic hair. No goiter was noted.

Craniofacial appearance

Microcephaly, oxycephaly, and midfacial hypoplasia were noted, as shown in Fig. 2a, b. Downturned corners of the mouth, deeply set eyes, lateral displacement of the inner canti, upslanting palpebral fissures, and prominent anthelix were also noted (Fig. 2c–e). In addition, narrow airway, tonsillitis, otitis media with mild hearing loss on the left side, and postoperative unilateral cleft lip and palate were also found (Fig. 2c, f, g).

Oral manifestations

Negative overjet and excessive overbite with large freeway space, caused by midfacial deficiency, were observed. Congenital absence of the maxillary lateral incisors and

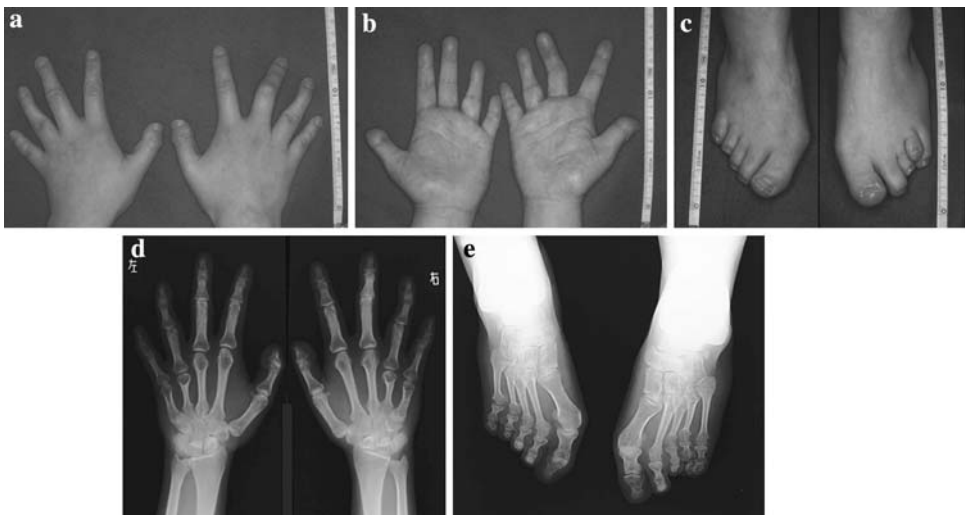

Fig. 1 Abnormalities of the hand and foot. The proximally placed thumbs, clinodactyly, short and tapered fingers (**a**, **b**), and feet deformity (**c**). Hand-wrist radiographs of both hands and feet (**d**, **e**)

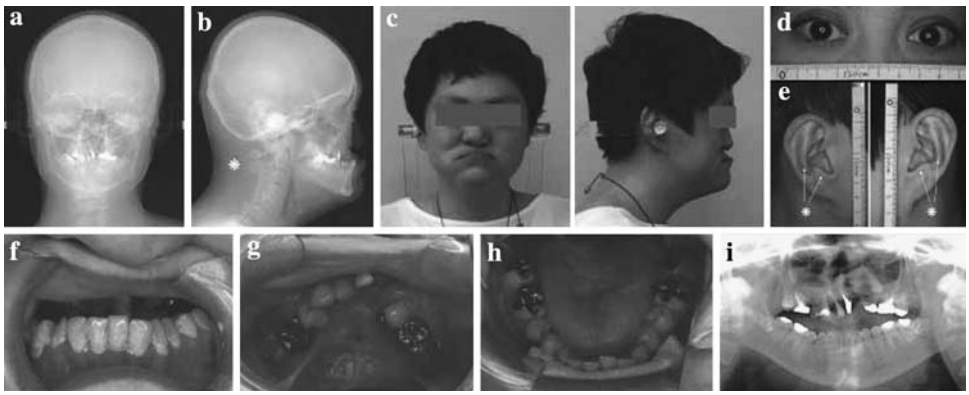

Fig. 2 Craniofacial appearance and oral manifestations. Cephalometric radiographs show microcephaly and oxycephaly, midfacial dysplasia, and vertebral fusion of C2–C3 (*asterisk*) (**a**, **b**). The midfacial hypoplasia, downturned corners of the mouth (**c**), deeply set eyes, lateral displacement of the inner canti, upslanting palpebral fissures (**d**), prominent anthelix (*asterisk*) (**e**), negative overjet and excessive overbite with a large freeway space, intermaxillary discrepancy with severe crossbite (**f**), left cleft lip and palate (**c**, **f**, **g**), and macroglossia (**h**). The multiple congenital missing teeth in the maxilla and impaction of the left canine in a panoramic radiograph (**i**)

second premolars on both sides, impaction of the maxillary left canine, and macroglossia were also seen (Fig. 2f–i).

Chromosomal findings

Chromosome analysis was performed on peripheral blood lymphocyte cultures and fibroblasts derived from periodontal ligament tissue of an extracted wisdom tooth. Standard G-bands by trypsin using Giemsa (GTG) analysis revealed 46,XX,del(18)(pter → q21.33:)[41], 46,XX,r(18)(::p11.21 → q21.33::)[8], and 46,XX,der(18)(pter → q21.33::p11.21 → pter)[1] in blood lymphocyte cells (Fig. 3a–c) and 46,XX, der(18)(pter → q21.33::p11.21 → pter)[50] in periodontal ligament fibroblasts (Fig. 3d). All cell lines appeared to be missing a portion of 18q (q21.33 → qter).

Fluorescence in situ hybridization (FISH) analysis for chromosome 18 (Fig. 3e–j; blood lymphocyte cells, k, l; periodontal ligament cells) was carried out using centromere- and subtelomere-specific probes. The 18p and 18q subtelomere-specific probes employed were Mixture 11 and Mixture 12 of ToTelVysion (Abbott Molecular Inc., USA.), respectively. Fifty metaphases of peripheral blood cells using 18p subtelomere-specific probes revealed ish 46,XX,18(18pterx1,D18Z1x1),del(18)(18pter−,D18Z1+)[41]/46,XX,18(18pterx1,D18Z1x1),r(18)(D18Z1+,18qter−)[8]/46,XX,18(18pterx1,D18Z1x1),der(18)(18pter++,D18Z1+)[1] (Fig. 3e–g). In 50 more blood lymphocyte cells, FISH using 18q subtelomere-specific probe, showed ish 46,XX,18(D18Z1x1,18qterx1),del(18)(D18Z1+,18qter−)[44]/46,XX,18(D18Z1x1,18qterx1),r(18)(D18Z1+,18qter−)[5]/45,XX,18(D18Z1x1,18qterx1)[1] (Fig. 3h–j). On the other hand, analysis of periodontal ligament cells using 18p and 18q subtelomere-specific probes in each 50 cells showed nonmosaicism, ish 46,XX,18(18pterx1,D18Z1x1,18qterx1), der(18)(18pter++,D18Z1+,18qter−) (Fig. 3k, l).

Discussion

A 27-year-old woman with de novo rod/ring mosaicism, dup(18p)/del(18q) and r(18), in peripheral blood cells is reported. De Pater et al. (2003) suggested that chromosome 18 might carry a high number of certain sequences, which are susceptible to interchromosomal as well as intrachromosomal rearrangements. The most frequent of these abnormalities are deletions and ring chromosome formation. Rings often appear as mosaics, as a consequence of the structural instability of the ring during cell division (Baumer et al. 2002; Miller et al. 2003). There have been reports of cases with chromosome 18 mosaicism, mostly involving chromosome 18 in different cell lines, including r(18), der(18), r(18)x2, monosomy 18 (Stankiewicz et al. 2001; De Pater et al. 2003; Miller et al. 2003; Carreira et al. 2007). Overall, these patients with r(18) often share clinical features with del(18q) syndrome, del(18p) syndrome, or their combination, depending on the size of the deletion. The incidence and type of congenital malformations in cases of r(18) are similar to those in patients carrying del(18)(q21-qter) (Schinzel 2001).

The exact mechanism of the mosaicism in our case is not known. The pattern of the dup(18p)/del(18q) seen in both peripheral blood cells and fibroblasts in the rod configuration raises the possibility of an inversion in chromosome 18 in one of the parents. However, no chromosomal anomaly was detected in either parent. Furthermore, the finding of an inversion would not explain the finding that the ring chromosome lacked the chromosomal material, p11.21 → pter, which is duplicated in the rod. Wyandt et al. (1982) reported rod/ring mosaicism of chromosome 2, and the most probable explanation is that the rod and ring configurations arose simultaneously from an intrachromosomal exchange. An isochromatid break in

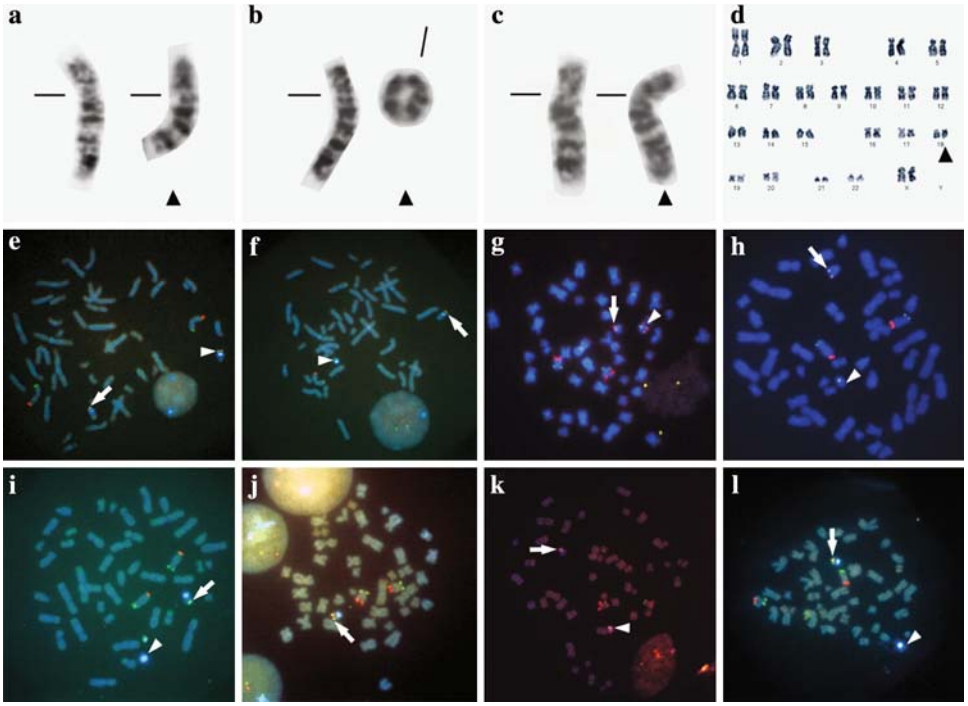

Fig. 3 Chromosomal analysis. Karyotypes of the patient by the G-banding method revealed 46,XX,del(18)(pter → q21.33:)[41], 46,XX,r(18)(::p11.21 → q21.33::)[8], and 46,XX,der(18)(pter → q21.33::p11.21 → pter)[1] in blood lymphocyte cells (**a**, **b** and **c**, respectively). Periodontal ligament fibroblasts (**d**) revealed 46,XX, der(18)(pter → q21.33::p11.21 → pter)[50]. *Bars* indicate centromere positions (**a**–**c**), and *arrowheads* abberant chromosomes (18) (**a**–**d**). Fluorescent in situ hybridization (FISH) analysis for chromosome 18 (**e**–**j**; blood lymphocyte cells, **k**, **l**; periodontal ligament cells) using centromere- and subtelomere-specific probes. The results with blood cells were: 46,XX,18(18pterx1,D18Z1x1),del(18)(18pter+,D18Z1+) (**e**); 46,XX,18(18pterx1,D18Z1x1),r(18)(18pter−,D18Z1+) (**f**); 46, XX,18(18pterx1,D18Z1x1),der(18)(18pter++,D18Z1+) (**g**); 46,XX, 18(D18Z1x1,18qterx1),del(18)(D18Z1+,18qter−) (**h**); 46,XX,18 (D18Z1x1,18qterx1),r(18)(D18Z1+,18qter−) (**i**); 45,XX,18(D18Z1x1, 18qterx1) (**j**). FISH analysis of periodontal ligament cells revealed ish 46,XX,18(18pterx1,D18Z1x1),der(18)(18pter++,D18Z1+)[50] for 18p subtelomere (**k**) and ish 46,XX,18(D18Z1x1,18qterx1),- der(18)(D18Z1+,18qter−)[50] for 18q subtelomere (**l**). *Arrows* indicate intact chromosomes 18 and *arrowheads* aberrant chromosomes 18. 18p (**e**–**g**, **k**) and 18q (**h**–**j**, **l**) subtelomere-specific probes employed were Mixture 11 and Mixture 12 of ToTelVysion (Abbott Molecular Inc., USA), respectively, as indicated by *yellow signals*, and 18cen by *blue signals*. Signals for chromosomes 11 (**e**–**g**, **k**) and 12 (**h**–**j**, **l**) were used as controls (*green* short-arm subtelomere, *red* long-arm subtelomere)

the long arm and a single chromatid break in the short arm of chromosome 18 were followed by rejoining of the broken ends to give dup(18p)/del(18q) and r(18) (Fig. 4). As a result, the chromosomal material, p11.21 → pter, was duplicated and deleted in the rod and ring configurations, respectively. On the other hand, the fragment q21.33 → qter was deleted from the long arm. Subsequent cell division would give rise to daughter cells representing the two cell lines in the patient. Differential selection against cells with the ring chromosome in blood and oral tissue probably occurred during subsequent embryological development. On the other hand, deletion of 18(p11.21 → pter) from the rod configuration, dup(18p)/del(18q), is speculated to be secondary, which deliver "del(18q)" (Fig. 3a) in peripheral blood cells. Additional cell lines have also been reported in lymphocyte cultures when compared with fibroblasts (Wyandt et al. 1982; Zahed et al. 2004). Modi et al. (2003) also reported mosaicism in peripheral blood but not in other tissues (buccal cells or amniocytes). One of 50 blood cells in our case showed 45,XX,−18. This cell line might have started as an r(18), and mitotic instability and crossing-over events between the ring sister chromatids led to its loss during cell division, which generated the monosomy. However, monosomy 18 might be considered as a culture artifact (Fischer et al. 2001; Schinzel 2001).

To determine the critical region for the del(18q) syndrome, a genotype–phenotype correlation has been studied (Kline et al. 1993; Brkanac et al. 1998; Cody et al. 1999). Zannolli et al. (2003) described a patient with del(18)(q21.31-qter) who had ectodermal dysplasia syndrome with a wide spectrum of abnormalities and a family pedigree with normal karyotypes, suggesting its subtle involvement in the development of ectodermal and/or mesodermal structures. Stewart et al. (2001) described another case of del(18)(q21.3) syndrome associated with harlequin ichthyosis, an autosomal recessive skin disorder, and speculated that the responsible gene may lie at or distal to 18q21.3. In a review of this syndrome, Schinzel (2001)

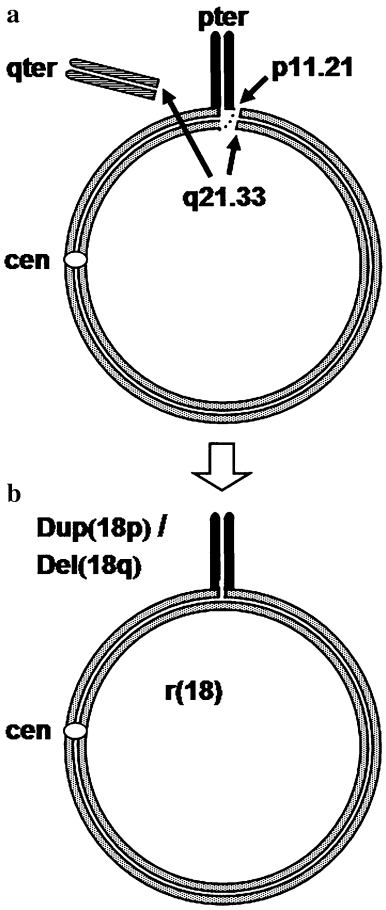

Fig. 4 Proposed mechanism of the rod/ring configuration. Intrachromosomal exchange involving an isochromatid break in the long arm and a single chromatid break in the short arm of chromosome 18. The *solid shaded* segment, p11.21 → pter, was duplicated and deleted in the rod and ring configurations. The *striped fragment*, q21.33 → qter, was deleted (**a**). Configuration after rejoining at the break points showing dup(18p)/del(18q) and r(18) (b). *cen*, centromere

described the presence of several less-common defects, such as brachycephaly, midface hypoplasia, coxa valga, and sparse hair. Zannolli et al. (2003) suggested that complex mechanisms may be involved in diversification of the neural crest, endoskeletal elements, brain organization, and the organization of other body parts, such as bones and teeth. The patient in our study also had several congenital abnormalities, including missing teeth; canine impaction; skin, hair, and nail dysplasia; vertebral fusion; and other skeletal and osteoarticular abnormalities. The association of a short neck in the absence of congenital heart defects may suggest the deletion of 18p material on ring chromosome 18 (Stankiewicz et al. 2001). However, such unique features might be explained by subtle involvement in the development of mesodermal structures. On the other hand, IgA deficiency, a common feature of chromosome 18p anomaly (Israels et al. 1996), has been reported in some cases of del(18q) (Hecht 1969) and ring chromosome (Burgio et al. 1980) but was not observed in this case.

Our patient had primary hypothyroidism due to Hashimoto thyroiditis and primary hypogonadism. Endocrine disorders have been reported, although rarely, in patients with del(18q) syndrome with similar breakpoints; a 4-year-old boy with type I diabetes and autoimmune thyroiditis who had a ring chromosome 18 (deletion 18q22.3-18qter) (Dacou-Voutetakis et al. 1999), and a 13-year-old girl with primary hypothyroidism who had a deletion of the long arm of chromosome 18 [del(18)(q21.3)] (Henrot et al. 1989). Therefore, it is possible to speculate that some gene(s) located on chromosome 18 are responsible for the polyglandular autoimmune process. Growth hormone deficiency and secondary hypogonadism in a boy with a ring 18 chromosome has been reported previously (Abusrewil et al. 1988). However, it was not the case in our study, where the patient had primary hypogonadism. Zahed et al. (2004) reported another case of an adult male with ring chromosome 18q and jumping translocation 18p who had partial primary hypogonadism as the sole phenotypic abnormality. The primary hypogonadism in our patient, a unique feature that has not been previously associated with r(18) of different sizes (Stankiewicz et al. 2001; Yardin et al. 2001; Baumer et al. 2002), may raise the possibility that deletion of the long arm of chromosome 18 may be responsible for the development of primary gonadal and thyroid failure. Such clinical traits in our case seem to be consistent with deletion in the long arm of chromosome 18.

This case shows an unusual cytogenic lesion; i.e., de novo rod and ring mosaicism. Further studies are needed to delineate the responsible critical regions and the genotype–phenotype relation in del(18q) syndrome.

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