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Trisomy 14pter→q21: A Case With Associated Ovarian Germ Cell Tumor and Review of the Literature

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We report a patient with trisomy X and a supernumerary marker chromosome. The marker chromosome was characterized by comparative genomic hybridization and shown to be derived from chromosome 14, resulting in trisomy for 14pter→q21. The karyotype was thus redefined as 48,XXX,+mar.rev ish enh(14pterq21). The patient presented with facial dysmorphism and a high-pitched cry, exhibited severe developmental delay, and developed an aggressive ovarian immature teratoma. In this paper, we also review reports of 11 other patients with constitutional trisomy of the same chromosomal region. Previous studies have identified somatic gains of chromosome 14 in ovarian germ cell tumors. We propose that the constitutional gain of chromosomal 14 material may have predisposed to the development of this tumor.

clude maternally derived duplications of the imprinted proximal 15q region with moderate to severe mental retardation, and duplication of proximal 22q11 in the cat eye syndrome [Crolla et al., 1998].

FISH using satellite (α , β , III) and ribosomal-DNA probes is useful for elucidating the origins of markers comprised predominantly of satellite DNA and/or heterochromatin. Comparative genomic hybridization (CGH) [Kallioniemi et al., 1992], matrix-CGH [Solinas-Toldo et al., 1997], micro-FISH [de Pater et al., 2002], and reverse chromosome painting [Carter, 1994] are useful techniques to detect the euchromatin content. They provide a more comprehensive analysis than conventional FISH, as they delineate the chromosomal regions involved, in addition to their origins and so may facilitate clinical syndrome delineation, or enable new syndromes to be described. These approaches promise to identify regions harboring disease-causing genes, detect cytogenetically cryptic rearrangements, and may be particularly beneficial in prenatal screening. In some circumstances, additional factors such as imprinting may need to be established before genotype-phenotype correlations are understood [Crolla et al., 1992].

The characterization of markers is also important as constitutional gains may be associated with tumor development. For over 60 years, it has been known that trisomy 21 patients have a 10–20-fold increased risk of developing leukemia [Fong and Brodeur, 1987; Sandberg, 1991]. More recently, constitutional trisomy 8 mosaicism has been associated with hematological neoplasms [Secker-Walker and Fitchett, 1995; Seghezzi et al., 1996; Maserati et al., 2002], and other constitutional chromosomal trisomies have been reported in individuals with a range of neoplasms (reviewed in Satge and Van Den, 1996). These observations suggest that constitutional trisomy may act as the first mutation in multistep carcinogenesis.

In the present study, we report the chromosomal origin of a SMC that was characterized in a patient with dysmorphic features, developmental delay, and an ovarian germ cell tumor (OGCT). The SMC was characterized by CGH, a molecular cytogenetic method for detecting changes in DNA copy number throughout the genome in a single hybridization.

INTRODUCTION

Genomic imbalances can cause mental retardation, congenital malformations, and miscarriages. While some imbalances are readily characterized by standard cytogenetic analysis others are small and require higher resolution approaches. Additionally there are many cases of individuals who have supernumerary marker chromosomes (SMCs), representing duplications of the genome, whose origins remain unknown. SMCs occur at a frequency of approximately 1.5/1,000 in humans [Sachs et al., 1987]. The phenotypic consequences of a de novo marker chromosome are difficult to predict. A study by Warburton [1991] identified abnormal phenotypes in 13% of probands bearing de novo markers, but no correlation could be derived between abnormal phenotype and the presence of satellited or nonsatellited markers. The very few established karyotype-phenotype correlations in-

CLINICAL REPORT

The proband was the second child of healthy, nonconsanguineous parents aged 42 (mother) and 37 (father), delivered by caesarian section at 41 weeks gestation due to non-progression of labor. The maternal obstetric history included one spontaneous abortion, and delivery by caesarian section of the older sibling. Resuscitation was required following birth. Cytogenetic analysis was requested in view of facial dysmorphism, together with a peculiar high-pitched cry. The facial features described at birth are listed in Table I,

and included a protruding tongue, slightly depressed nasal bridge, and hypertelorism. Other features noted at birth included narrow upper airway, increased space between first and second toes, short thick neck, pendulous abdomen with umbilical hernia, hypotonia, and persistent fisting, low birth weight (<3rd percentile), microcephaly (<3rd percentile), and short stature (<3rd percentile) (Table I).

Breathing and feeding problems and mild jaundice were noted in the neonatal period. The patient was extremely irritable and cried extensively throughout the early years of life. She perspired excessively. Seizures were noted by 9 months. Delayed development became apparent rapidly. At 2 years, her developmental quotient was measured at 51, and personal/social scale at 29. She was only able to walk with a rollator at 6 years of age. Mobility was compromised by hypermobility of the knees and by inversion of the left foot, so that she stood on the medial malleolus. A cliky right hip was also noted, but this was normal on X-ray. No neuromuscular abnormality was found. Although she was eventually able to walk independently for a few yards, by the age of 15 years she was confined to a wheelchair as a consequence of obesity and unwillingness to walk.

She had premature thelarche, <8 years of age. At 8 years of age, thick hair, deep-set eyes, very straight eyebrows and retrognathia with dimple were apparent (Fig. 1a), but the previously described hypertelorism and depressed nasal bridge were not apparent. She remained mute and doubly incontinent throughout her life. Short stature and recurrent upper respiratory infections were persisting features.

At 16 years, a right ovarian mass was diagnosed. Surgical resection revealed a 20-cm tumor without a true capsule and covered with hemorrhagic omentum. Histopathological examination revealed a stage 3C undifferentiated malignant ovarian teratoma of yolk sac origin with local extension. The tumor showed a highly variable and pleomorphic morphology. It was composed of poorly differentiated to undifferentiated adenocarcinoma, with some papillary formation and a component with a clear cell lace-like pattern, Schiller Duval bodies, hemorrhagic zones, and giant cells suggestive of trophoblast. Elevated tumor markers included CA-125 at 221 U/ml (0–35), alpha-fetoprotein at 2,514 KU/L (0–10), and HCG 7 IU/L (0–5). Local tumor recurrence occurred rapidly after an initial response of residual disease to chemotherapy and the patient died.

MATERIALS AND METHODS

Cytogenetics and Molecular Cytogenetics

Metaphase spreads were prepared from short-term phytohemagglutinin-stimulated lymphocyte cultures performed shortly after birth, and repeated on short-term cultures of the tumor specimen when the teratoma was resected. They were harvested and stained by G-banding, Quinacrine, and DAPI using standard methods [Rooney and Czepulkowski, 1986]. FISH studies were performed on the tumor specimen using a Y whole chromosome paint (Cambio, UK) according to the manufacturer's instructions, to exclude the presence of Y chromosome euchromatin since, prior to histopathological analysis, the possibility of gonadoblastoma had not been excluded [Lau, 1999]. The origin of the marker was determined by CGH. DNA was extracted from the tumor culture using the QIAamp DNA mini kit (Qiagen, Crawley, UK). DNA from the tumor and reference DNA were labeled with spectrum green-dUTP and spectrum red-dUTP by nick translation (Vysis, UK). CGH was performed according to the manufacturer's instructions. The labeling was reversed to confirm the findings. CGH analysis was performed using the Cytovision FISH Workstation (Applied Imaging, Newcastle, UK).

RESULTS

Cytogenetics and Molecular Cytogenetics

G-banding of constitutional lymphocytes, revealed an abnormal karyotype in all cells analyzed ($n = 23$) with trisomy X and a marker chromosome, 48,XXX,+mar (Fig. 1b). The parental karyotypes were normal and therefore established the marker to be de novo. Cytogenetic analysis of the cultured tumor cells revealed the same cytogenetic abnormalities as had been identified constitutionally. The marker chromosome was negative for DAPI, Quinacrine, Y whole chromosome paint, did not contain satellites associated with nucleolus-organizing regions (data not shown), and was of similar size to a G-group chromosome. CGH showed gains of the entirety of X, attributable to the trisomy X, and of 14pter→q21, indicating the origins of the SMC (Fig. 1c). Loss of Y chromosome was also evident, consistent with the sex of the proband. The karyotype was thus redefined as 48,XXX,+mar.rev ish enh(14pterq21).

DISCUSSION

Trisomy 14pter-q21: Clinical Phenotype Correlations

In order to identify clinical features associated with dup(14pterq21) we reviewed the published literature for similar cases (Table I). We found no cases of de novo SMCs containing similar chromosomal segments. All previously reported cases known to be trisomic for 14pter→q21 originated from balanced parental translocations. In addition to the proximal trisomy 14, every case had an additional region of genomic imbalance (duplications in all but one case). It is extremely likely that these additional genomic imbalances will have had additional phenotypic effects making karyotype-phenotype correlations difficult (Table I). Trisomy of 14pter→q21 is associated with adverse phenotypic effects (Table I), but is compatible with life, whereas trisomy of the entire chromosome appears lethal [Kajii et al., 1972]. Phenotypic variability has been noted between siblings who have identical chromosomal rearrangements of this region (Table I, see cases reported by [Surana et al., 1974; Pena et al., 1976; Miller et al., 1979]). Many non-specific features seen in the present case were also shared by patients with partial proximal trisomy 14 with different or undefined breakpoints. These include abnormal cry [Allderdice et al., 1971; Reiss et al., 1972; Short et al., 1972], extensor rigidity [Short et al., 1972], irritability [Pena et al., 1976], and recurrent infections [Fryns et al., 1974; Yeatman and Riccardi, 1976]. The effect of partial trisomy 14 on puberty is unclear as delayed puberty in males [Smith et al., 1980; Valkova and Stefanova, 1993], amenorrhoea [Callen et al., 1992], early breast development (current case), and precocious puberty [Muldal et al., 1973] have been described. Some features have been reported only in single cases of trisomy 14pter→q21. These include widely spaced nipples [Fried et al., 1980], inguinal hernia [Giorgi et al., 1979], and sloping shoulders [Giorgi et al., 1979]. Our case had very straight eyebrows similar to the appearance in terminal deletion 1p36 syndrome [Heilstedt et al., 2003]. However, analysis of photographs of previously reported cases with dup(14)(pterq21) has shown this feature to be consistent [Giorgi et al., 1979; Smith et al., 1980]. Patchy depigmentation was present in two cases [Turleau et al., 1975; Valkova and Stefanova, 1993].

There are also numerous reports of subjects with proximal partial trisomy 14 in whom the breakpoints have not been characterized [Reiss et al., 1972; Short et al., 1972; Muldal et al., 1973; Tada et al., 1982], or that do not correspond to the trisomic region in our proband (trisomy 14pter→q13 [Laurent et al., 1973; Coco and Penchaszadeh, 1977; Abeliovich et al.,

TABLE I. Summary of Features Associated With Trisomy 14pter→q21 in our Case and in Previous Reports

	Fried et al. [1980]	Smith et al. [1980]	Simpson and Zellweger [1977]	Turleau et al. [1975]	Valkova and Stefanova [1993], case 2 ^a	Miller et al. [1979]; four cases	Giorgi et al. [1979]; one case at 2 ages; 4 wk and 8 yr
Karyotype	46,XXX,-22,+der(14)t(14;22)(q21;q11)	47,XX,+der(14)t(3;14)(p25;q21)	47,XX,+der(14)t(3;14)(q29;q21)	47,XX,+der(14)t(12;14)(q24;q21)	47,XX,+der(14)t(2;14)(q36;q21)	47,+der(14)t(9;14)(p24;q21)	47,XX,+der(14)t(10;14)(p15.2;q21)
Regions of genomic imbalance	Dup(14pter→14q21)	Dup(14pter→14q21)	Dup(14pter→14q21)	Dup(14pter→14q21)	Dup(14pter→14q21)	Dup(14pter→14q21)	Dup(14pter→14q21)
Age at examination	19 mth	18 yr	14 mth	18 mth	13 yr	0-3 yr, ND, 2 yr, 30 mths	4 wk 8 yr
Eye anomalies	Small palpebral fissures	Deep-set eyes, small palpebral fissures	Epicanthic folds, hypertelorism, palpebral fissures slant down, ptosis of eyelids	Hypotelorism	Asymmetric eyes, enophthalmos, hypotelorism	Palpebral fissures slant down at 4 wk, slant up at 8 yr; strabismus/gaze palsy at 8 yr	Palpebral fissures slant down at 4 wk, slant up at 8 yr; strabismus/gaze palsy at 8 yr
Nose anomalies	Flat nasal bridge	Convex profile of nose, wide nasal bridge	None	Large nose	Anteverted nares, large nose, thin nasal bridge	Wide nasal bridge (4/4), flat nasal bridge (4/4), bulbous tip of nose (4/4), prominent nostrils (2/4), wide alae (4/4)	4 wk: anteverted nares, large nose, wide nasal bridge, bulbous tip of nose 8 yr: none
Mouth anomalies	None	Arched shape	Bifid uvula, arched shape, down-turned corners of mouth, high palate, narrow palate	Cleft palate, arched shape, down-turned corners of mouth, macrostomia	Irregular teeth, thin upper lip, thin lower lip	Cleft of lower lip (1/4), cleft palate (2/4), arched mouth (4/4), down-turned corners of mouth (4/4), high palate (1/4), thin lower lip (1/4), thin upper lip (1/4), vermilion border on upper lip (1/4), open mouth appearance (4/4)	Microstomia at 4 wk, macrostomia and thin upper lip at 8 yr
Ear anomalies	None	Dysplastic, low-set	Low-set	None	Low-set	Simple helix (2/4)	Dysplastic, low-set, prominent helix and middle antihelix at 4 wk. None at 8 yr.
Other facial features	Microcephaly, protruding tongue	Protruding tongue, round face, retrognathia	Plagiocephaly, microcephaly	None	Asymmetric face, microcephaly, poorly defined philtrum, micrognathia	Microcephaly (4/4), short philtrum (4/4) oxycephaly (4/4), micrognathia (3/4).	4 wk: brachycephaly, flat occiput, frontal bossing, long philtrum, low frontal hairline, micrognathia 8 yr: frontal bossing, flat occiput
Hand anomalies	None	Clinodactyly, abnormal palmar crease	None	None	Single palmar crease	Clinodactyly (4/4), distal digital hypoplasia (4/4), posterior dislocation of radial heads (1/4), Simian palmar crease (4/4), syndactyly (1/4)	4 wk: none 8 yr: clinodactyly
Foot anomalies	Club foot, plantar flexion of toes	None	Metatarsus adductus	Pes equinovarus	Isodactylism of toes, over-riding toes	None	4 wk: none 8 yr: club foot
Psychomotor anomalies	Mental retardation, seizures, no speech	Mental retardation, seizures	Mental retardation, motor subnormality	Mental retardation, seizures, motor subnormality	Mental retardation, no speech	Mental retardation (4/4), seizures (3/4), motor subnormality (4/4), spastic quadripareisis (1/4), ataxic gait (1/4)	4 wk: mental retardation, motor subnormality, 8 yr: mental retardation, motor subnormality, cerebral palsy, ataxic paraparetic gait, limited speech
Musculo-skeletal anomalies	Hypotonia, dislocation of hip, hypermobile knee joints, extensor rigidity	None	Hypertonia, hypotonia	Hypotonia, osteoporosis	Hypertonia	Hip dislocation (1/4), hypertonia (1/4), hypotonia (1/4), pectus excavatum (1/4), 11 sets of ribs (1/4)	4 wk: none 8 yr: delayed skeletal maturation, hypertonia, kyphosis, pectus carinatum

(Continued)

TABLE I. (Continued)

	This report	Fried et al. [1980]	Smith et al. [1980]	Simpson and Zellweger [1977]	Turleau et al. [1975]	Valkova and Stefanova [1993]; case 2*	Miller et al. [1979]; four cases	Giorgi et al. [1979]; one case at 2 ages; 4 wk and 8 yr.
Other features	Short stature, proportionate, low birth-weight (<3rd centile), short, broad neck, irregular sleep pattern, apnea, constipation, protuberant abdomen, umbilical hernia	Short neck	Short stature, proportionate, low birth-weight (<3rd centile), short, sacral dimple, protuberant abdomen	Short stature, proportionate, low birth-weight (<3rd centile), short neck	Short stature, proportionate, low birth-weight (<3rd centile), short, broad neck, protuberant abdomen	Short stature, proportionate, low birth-weight (<3rd centile), short neck, sacral dimple	Short stature, proportionate (4/4), low birth-weight (<3rd centile) (3/3, ND for 4th), short neck (1/1), ND for others, sacral dimple (1/1) ND for others, umbilical hernia	Short stature, proportionate (8 yr), but not at 4 wk. 4 wk: short, broad neck, absent at 8 yr. Umbilical hernia present at 8 yr. (absent at 4 wk)

Case 1 of Valkova and Stefanova [1993] was excluded because little clinical information was available, presumably due to death at 1 years of age. Features noted were facial dysmorphism and bilateral Simian creases. ND = no data available, mth = month, yr = year, wk = week.

1982; Faugeras and Barthe, 1986]; trisomy 14pter→14q22 [Fawcett et al., 1975; Raoul et al., 1975; Cohen et al., 1976; Pena et al., 1976; Yeatman and Riccardi, 1976; Lancet et al., 1981]; trisomy pter→q24 [Cottrall et al., 1981]), and reports of SMCs shown by FISH to originate from chromosome 14 [Crolla et al., 1992, 1998]. A similar facial appearance is found in individuals with trisomy 14pter→q21, q22, and q23 [Miller et al., 1979]. The clinical features depend on not only the region of chromosome 14 involved, but also on any additional trisomic or monosomic segments [Tada et al., 1982; Orellana et al., 2001].

The more consistent clinical features of proximal trisomy 14 include psycho-motor retardation, seizures, low birth-weight, short stature, short neck, microcephaly, small/sloping palpebral fissures, micropthalmia, hypo/hypertelorism, low-set ears, dysplastic ears, arched mouth (thin and downturned),

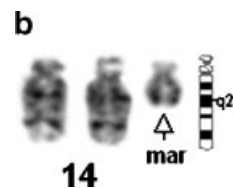


Fig. 1. a: Photograph of the proband aged 8 years to illustrate the facies. b: Ideogram of chromosome 14 and G-banded SMC and normal chromosome 14 homologues present in proband, (c) CGH profile showing gains of 14pter→14q21 and Xpter→Xqter, corresponding to the SMC and trisomy X, and loss of the Y chromosome.

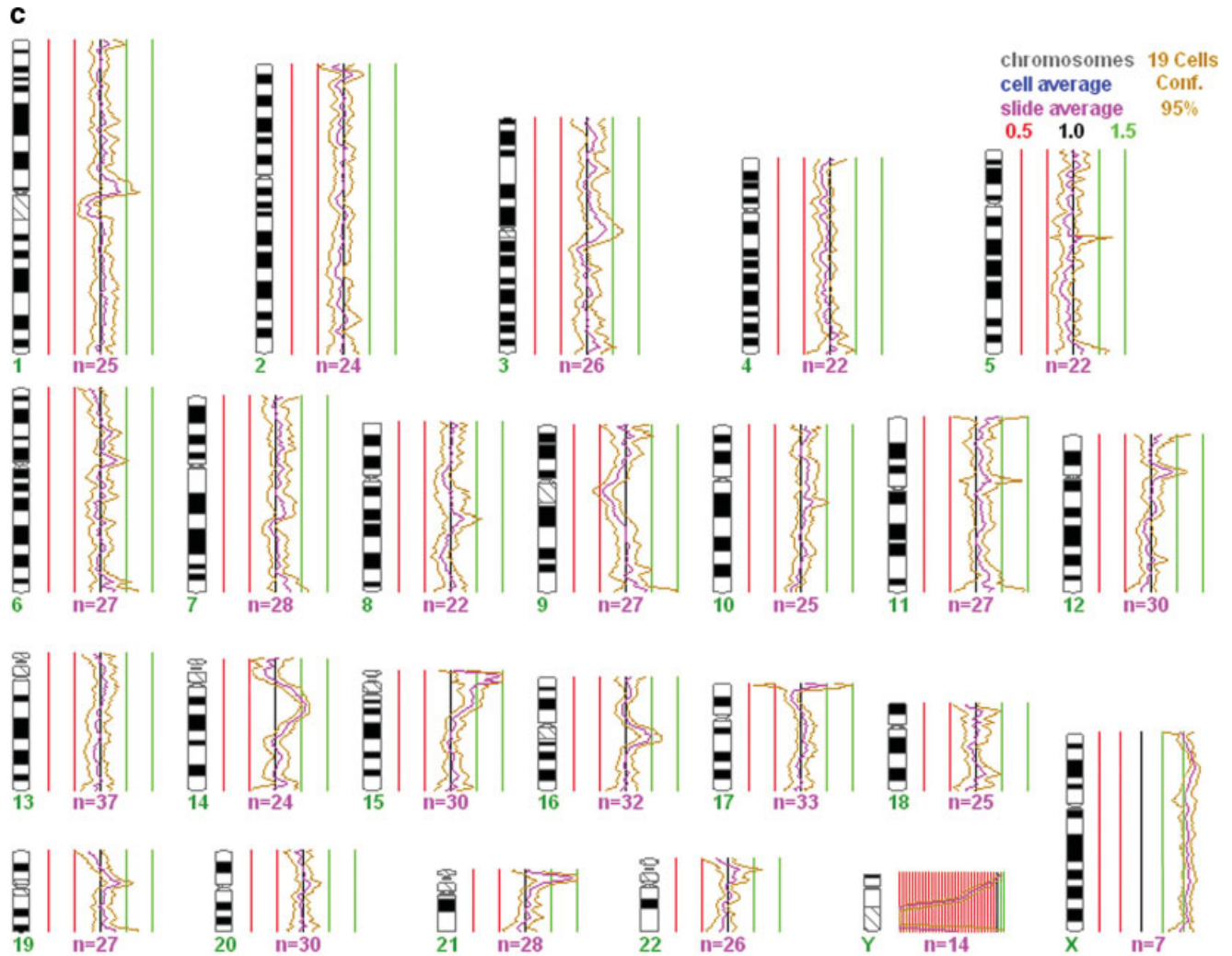


Fig. 1. (Continued)

wide mouth, cleft palate or alveolar ridge, micrognathia, prominent nose, broad flat nasal bridge, short/long philtrum, clubfeet, clinodactyly, camptodactyly, flexion contracture, rib anomalies, cardiac anomalies, cryptorchidism, irritability, feeding difficulties, and recurrent respiratory infections (Table I) [Pena et al., 1976; Simpson and Zellweger, 1977; Johnson et al., 1979; Miller et al., 1979; Fried et al., 1980; Smith et al., 1980; Tada et al., 1982].

In addition to the SMC, trisomy X was found constitutionally in the current case. Triple X syndrome females usually have no serious physical abnormalities but can show reduced intelligence (70% of cases), and occasionally behavioral problems. The gonads and sexual development are usually normal [Harper, 1998; Nussbaum et al., 2001; Mueller and Young, 2003]. Genitourinary developmental abnormalities and tumors are rare [Hoang et al., 1999], with the few published exceptions including malignant stromal tumor of the ovary [Khoo and Buntine, 1980] and ovarian dysgenesis [Fryns et al., 1983; Spear and Porto, 1988]. The majority of clinical features in the present case are likely to be attributable to the SMC.

Trisomy 14 and OGCT

To our knowledge, this is the first report of a female with a SMC derived from chromosome 14 who has developed an

OGCT. There are no reports of testicular germ cell tumors (TGCT) in males with trisomy proximal 14. However, there are accounts of undescended testis [Crolla et al., 1992] and infertility [Gentile et al., 1993] in such individuals, both of which are risk factors for TGCT [United Kingdom Testicular Cancer Study Group, 1994].

The karyotype obtained from the teratoma was the same as the constitutional karyotype. This is consistent with the low number of genomic changes (average of 1.4), found in immature teratomas by CGH as compared with the other subtypes of malignant OGCTs (dysgerminomas and endodermal sinus tumors showed 10 and 6, respectively) [Kraggerud et al., 2000]. Trisomy 14 is a common recurrent chromosomal abnormality in malignant OGCT, found in 6/24 OGCT present in 10–14 year olds [Bussey et al., 1999]. It has been reported as a sole abnormality in four cases studied by conventional cytogenetics [Ihara et al., 1984; King et al., 1990; Bussey et al., 1999]. Trisomy 14 was also identified by CGH in one case of immature grade III teratoma [Rioped et al., 1998], the same tumor type as in the present case. Structural rearrangements of chromosome 14 have also been found in OGCT including $\text{dup}(14)(q11q22)$ [Jenkyn and McCartney, 1987] and $\text{t}(8;14)(q11;q11)$ [Noumoff et al., 2001]. Interestingly, one case of OGCT has been reported in a patient with constitutional trisomy X with trisomy 14 as a somatic change in the tumor

[Bussey et al., 1999]. Furthermore, gains of X chromosome are common in TGCT and extragonadal GCT [Mitelman, 1994; Summersgill et al., 1998; Rosenberg et al., 1999] and Klinefelter's syndrome (47,XXY) patients show an increased incidence of GCT.

There are few detailed reports of the clinical findings in proximal trisomy 14, and to our knowledge only the present case has developed an OGCT. However this is the oldest case reported, the other being 8 years of age or less at reporting [Giorgi et al., 1979]. More thorough characterization of SMCs, for example by CGH, will help to clarify whether constitutional proximal trisomy 14 predisposes to OGCT.

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