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A Case of Partial Trisomy 2p23-pter Syndrome with Trisomy 18p Due to a *de novo* Supernumerary Marker Chromosome

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Partial trisomy 2p is a rare but relatively well-defined syndrome with distinctive clinical features, including marked psychomotor delay, dysmorphic face, and congenital heart disease. The phenotype of trisomy 18p is variable, from normal appearance to moderate mental retardation. Most cases of trisomy 2p and trisomy 18p result from the inheritance of an unbalanced segregant from a balanced parental translocation or due to *de novo* duplication. Here, we present the first report of a combined partial trisomy 2p and trisomy 18p due to a supernumerary marker chromosome (SMC). The final karyotype of the patient was 47,XX,+der(18)t(2;18)(p23.1;q11.1)[22]/46,XX[8]. The patient had typical dysmorphic features of partial trisomy 2p23-pter syndrome and congenital heart disease. SMCs are remarkably variable in euchromatic DNA content and mosaicism level. The precise identification of the origin and composition of SMCs is essential for genotype-phenotype correlation and genetic counseling. *(Korean J Lab Med 2010;30:312-7)*

Key Words : *Partial trisomy 2p23-pter, Trisomy 18p, Supernumerary marker chromosome*

INTRODUCTION

A supernumerary marker chromosome (SMC) is defined as a structurally abnormal chromosome that occurs in addition to the 46 normal chromosomes, and that cannot be unambiguously identified or characterized by conventional banding cytogenetics [1]. The prevalence of SMC is 0.4-1.5/1,000 in prenatal diagnosis and 0.66/1,000 in newborns, with a higher frequency in mentally delayed populations (3.27/1,000) [2]. SMCs are associated with phenotypic heterogeneity and even found in phenotypically normal individuals. When an SMC is diagnosed, predicting the risk associated with an abnormal phenotype remains difficult, especially for *de novo* cases [3]. The clinical variability among SMCs may be attributed to their size, the presence of euchromatic material, the degree of mosaicism, and/or the uniparental disomy. Therefore, the precise characterization of SMCs is essential in order to perform genotype-phenotype correlation and predict the prognosis [4, 5]. Here, we present a case of SMC that was proved to be der(18)t(2;18)(p23.1;q11.1) by array comparative genomic hybridization (aCGH). The patient had typical phenotype characteristics of partial trisomy 2p23-pter syndrome. To our knowledge, this is the first report of a combined partial trisomy 2p and trisomy 18p due to an SMC.

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CASE REPORT

1. Clinical features

A female newborn was admitted for the evaluation of

intrauterine growth retardation and dysmorphic features. She was the first child of nonconsanguineous parents. At birth of the infant, the mother and father were 31 and 39 yr old, respectively. The infant was born at 38^{+1} weeks of gestation by cesarean delivery due to placenta previa. The birth weight of 2,700 g was adequate for the gestational age, but after diuretic treatment, the weight declined to 2,150 g (under tenth percentile). Head circumference was initially 35.7 cm (>90th percentile) but became as low as 32 cm (10-25th percentile) after scalp edema improved. She was immediately intubated because of respiratory distress. Initial X-ray showed total lung haziness, and surfactant was used despite full-term gestation. She was noted to have dysmorphic features (prominent occiput, high-arched palate, short nose with anteverted nares, orbital hypertelorism, depressed nasal root, low set ears, small hands with widened finger-tips, and spooned nails) and a congenital heart defect. Echocardiogram showed a perimembranous-type ventricular septal defect of 5 mm and a secundum atrial septal defect of 4 mm, with right atrial enlargement and right ventricular hypertrophy (Table 1). Laboratory results for congenital TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus) infection were negative, and newborn metabolic screening was normal. Ophthalmologic examination was unremarkable, except for chorioretinal degeneration.

Table 1. Main clinical features in patients with partial trisomy 2p23-pter syndrome

Main clinical features in 2p23-pter trisomy	Present case
Severe mental retardation	+
Growth deficiency	+
Prominent high forehead with frontal upsweep of hair	+
Hypertelorism	+
Ptosis	-
Nasolacrimal duct obstruction	-
Wide nasal bridge	+
Short nose	+
Maxillary hypoplasia	-
Micrognathia	+
Low-set ears	+
Long tapering fingers/toes	+
Scoliosis	-
Hypoplastic external genitalia	-
Heart defect	+
Diaphragmatic hernia	-
Neural tube defects	-
Neuroblastoma	-

At 7 months, the infant still showed growth retardation, and her height and weight were less than third percentile. She was neither able to turn over nor sit without support. She also showed moderate mental and psychomotor developmental delay according to the Korean Bayley Scales of Infant Development-II [6].

2. Cytogenetic study, array comparative genomic hybridization, and FISH

Cytogenetic study was performed using phytohemagglutinin-stimulated lymphocyte culture with peripheral blood. Routine G-banded chromosome analysis showed a female karyotype with an SMC in 22 of the 30 cells examined (Fig. 1). Parental karyotypes were analyzed, and both of them had a normal karyotype, rendering this a *de novo* chromosomal abnormality. To define the marker chromosome, a whole genomic array comparative genomic hybridization (aCGH) analysis was performed with 4,500 selected bacterial artificial chromosomes (MacArray™ Karyo 4,500; Macrogen Inc., Seoul, Korea). In aCGH, a gain of 46 and 30 clones on 2p23.1-pter and 18p11.32-18q11.1, respectively, was observed. The duplicated region in chromosome 2 covered 21.5 Mb (18,179-21,517,981 bp), and the duplicated region in chromosome 18 covered 17.0 Mb (59,690-17,039,831 bp) (Fig. 2). We could not perform aCGH of her parents because they declined additional stud-

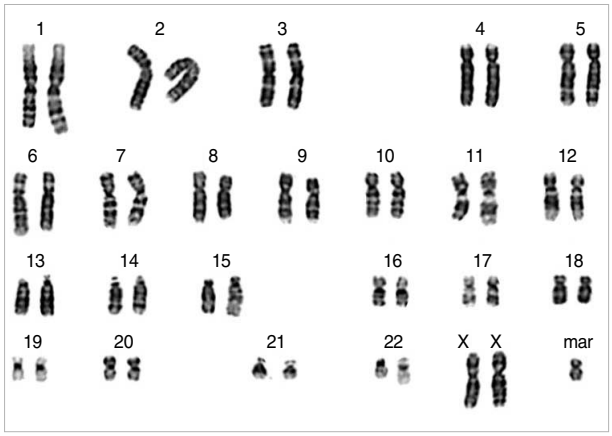

Fig. 1. The representative karyotype showing 47,XX,+mar (GTG banding, ×1,000).

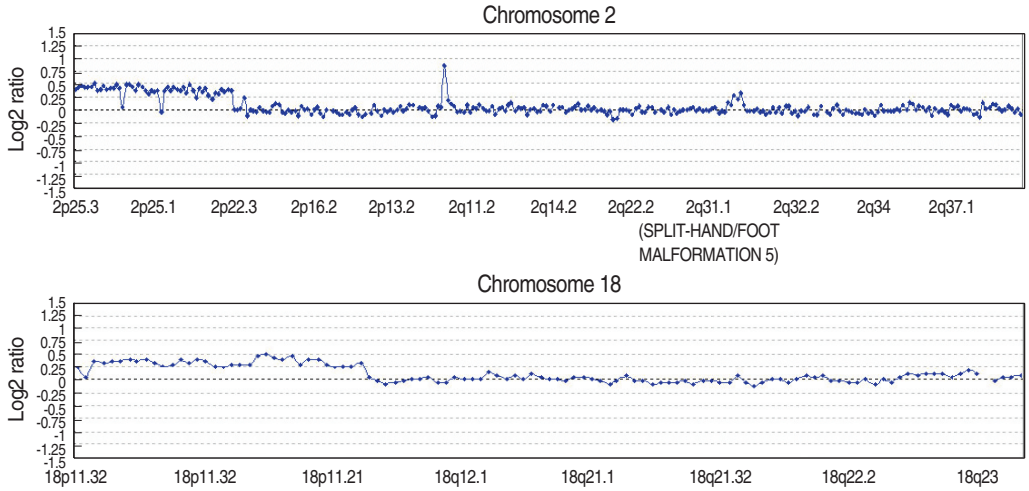

Fig. 2. The ratio plots from array comparative genomic hybridization (aCGH) for chromosomes 2 and 18. The test sample was labeled with cyanine 3, and the reference sample was labeled with cyanine 5. Log2 ratio was calculated as log2(cy3)-log2(cy5), and a gain of particular clone is manifested as an upward deviation from the modal value 0.25. Gain of 46 clones on 2p and 30 clones on 18p were observed. The result of aCGH revealed arr 2p25.3p23.1(18,179-21,517,981)×3,18p11.32-18q11.1(59,690-17,039,831)×3.

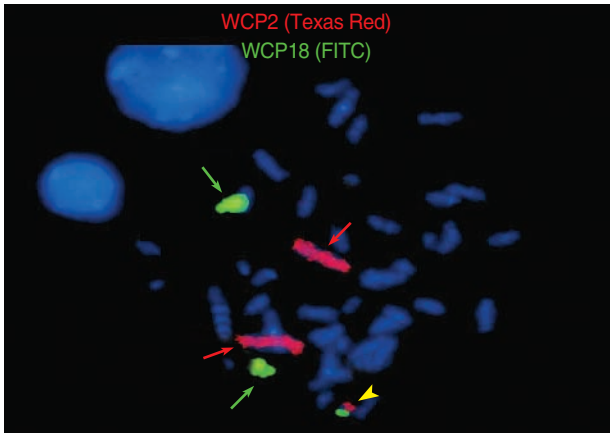

Fig. 3. FISH using whole chromosome painting probes (×1,000) of chromosomes 2 (labeled with Texas Red) and 18 (labeled with FITC) showed 2 signals of chromosomes 2 (red arrows), 2 signals of chromosome 18 (green arrows), and a small derivative chromosome comprising chromosomes 2 and 18 (yellow arrowhead).

ies. For the validation of the gain predicted by aCGH, FISH analysis was performed using whole chromosome painting probes of chromosomes 2 and 18 (WCP2 and WCP18; Cytocell Ltd., Cambridge, UK), and the marker chromosome was found to comprise parts of chromosomes 2 and 18 (Fig. 3). The karyotype of the patient was confirmed to be 47,XX,+der(18)t(2;18)(p23.1;q11.1)dn.ish der(18)t(2;18)(wcp2+,wcp18+).arr 2p25.3p23.1(18,179-21,517,981)×3,18p11.32-18q11.1(59,690-17,039,831)×3, according to the International System for Human Cytogenetics Nomenclature, 2009 [7].

DISCUSSION

The partial trisomy 2p syndrome is a rare constitutional aneuploidy in humans. It was first described by Francke and Jones [8] and has been reported in over 60 cases [8, 9]. Trisomy 2p could arise as a result of malsegregation of balanced parental translocation, or less frequently, due to *de novo* duplication or addition to another chromosome. Although an unbalanced translocation implies partial monosomy of other chromosomes, the clinical phenotype is consistent with pure partial trisomy 2p despite the fact that another chromosome is involved in the rearrangement. The patients who have trisomy 2p23-pter share distinctive clinical features, including marked psychomotor delay, dysmorphic features with high forehead, frontal bossing, short nose with anteverted nares, hypertelorism, malar hypoplasia and micrognathia, and skeletal anomalies such as scoliosis, long tapered fingers, and congenital heart disease (Table 1) [9-13]. Here, we present a case of SMC with the clinical features of classical partial trisomy 2p23-pter. The marker chromosome was identified as der(18)t(2;18)(p23.1;q11.1). On the basis of literature review, this is the first report of partial trisomy 2p

syndrome due to an SMC and trisomic component of another chromosome.

Psychomotor abnormality and mental retardation are common manifestations of partial trisomy 2p. Several genes that were thought to be putative genes associated with the development of the central nervous system (CNS) were mapped on 2p, such as human *SOX11* and *MYT1L* genes on 2p25.3. Both the genes are predominantly expressed in the developing CNS, suggesting an important role in neuronal maturation and differentiation [14, 15]. The *ALK* gene on 2p23.2 that encodes a receptor tyrosine kinase is also considered to play an important role in the development of the brain [16]. Although the association of mental retardation and duplication of these genes is not clear, the deletion of *SOX11* and duplication of *MYT1L* have been recently reported in patients with mental retardation or deficit schizophrenia [17, 18].

Interestingly, 4 cases of neuroblastoma with partial trisomy 2p have been reported. It was postulated that a germ-line duplication of 2p, yielding 3 copies of *MYCN*, may have predisposed those cases to the development of a neuroblastoma. *MYCN* is known to be a proto-oncogene that is localized to 2p24.1-24.3 [19]. Our patient also gained *MYCN*; hence, we recommended abdominal ultrasonography (US) every 6 months.

Trisomy 18p has rarely been reported. The implication of additional trisomy 18p in this patient is not clear. The mechanism and size of the chromosomal segment of the partial trisomy 18p and phenotypic expression varies markedly from normal to moderate mental retardation; hence, trisomy 18p does not seem to be a specific phenotypic entity. Although, euchromatic autosomal trisomies are generally associated with physical malformations and/or mental retardation, about 35-50% patients with partial trisomy 18p had a normal phenotype with normal intelligence [20]. This may be the reason why this trisomy has seldom been reported. Most cases of trisomy 18p have resulted from the inheritance of an unbalanced segregant from a balanced parental translocation, and the phenotype in those cases was not only due to the trisomy 18p but also influenced by the partial monosomy in the derivative chromosome. Moreover, the phenotype of trisomy 18p is variable even in isolated trisomy 18p cases due to an SMC or duplication [21, 22]. It is generally accepted that trisomy 18p does not have important clinical repercussions, whereas tetrasomy 18p due to extranumerary i(18)p is considered as a clinically distinct syndrome involving mental retardation; microcephaly; dolichocephaly; craniofacial features, including low-set ears, upslanting and short palpebral fissures, high-arched palate, delicate face with small or pinched nose, and small mouth; and skeletal findings, including scoliosis and feet malformation [23].

SMCs can arise from all human chromosomes. Euchromatic DNA content and mosaicism level of SMCs are variable. Approximately 70% of SMCs arise *de novo*, with 20% maternal and 10% paternal inheritance [24]. Familial marker chromosomes are usually harmless if they have been inherited from a phenotypically normal parent [25], but the clinical outcome is difficult to predict in cases with a *de novo* SMC. The risk for a *de novo* SMC to produce an abnormal phenotype has been estimated to be about 13-26% in unselected children group or prenatal cases [26, 27]. The clinical manifestation of SMCs seemed to depend on the presence of euchromatin and the chromosomal origin [4, 5]. According to the meta-analysis of published cases, isochromosome 12p, isochromosome 18p, and inv dup(22q) were correlated with known clinical syndromes. SMCs derived from chromosome 15 [SMC(15)] represented the most common SMCs, and 50% of the carriers of SMC(15) were healthy. However, only 8% of the carriers of SMCs derived from other chromosomes showed no clinical symptom. Clinical abnormalities seemed to be unrelated to the level of mosaicism [4]. Starke et al. [5] reported that small proximal trisomies of 1p, 1q, 2p, 6p, 6q, 9p, and 12q seem to lead to clinical manifestations, whereas partial proximal trisomies of 2q, 3p, 3q, 5q, 7p, 8p, 17p, and 18p may not be associated with significant clinical symptoms. Hence, the precise identification of the origin and composition of SMCs is essential for genetic counseling. Use of aCGH is time-saving and cost-effective compared with the use of multiple FISH probes for the identification of chromosomal origin and accurate delineation of duplicated regions

[28]. The aCGH technique should facilitate precise genotype-phenotype correlation and prediction of the clinical outcome [13].

In summary, we described the first case of partial trisomy 2p23-pter and trisomy 18p due to an SMC. Partial trisomy 2p rather than trisomy 18p may be responsible for the clinical manifestations in our patient. Because a neuroblastoma is regarded as a common manifestation of trisomy 2p and our patient showed gain of *MYCN* gene, we recommend careful observation in such patients.

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