票のコピー1部について個人情報管理者が管理した。個人情報と匿名化後のIDを連結する対応表はコンピューターの外部記憶装置に保存し、鍵のかかるキャビネット内で個人情報管理者が保管した。試料等に関するデータベースをコンピューターを用いて取り扱う場合は、インターネットや他のコンピューターから切り離した状態で取り扱った。

## C．研究結果

マイクアロアレイ染色体検査で過去に報告の無いXq22の約3-Mbの微細欠失を認めた。両親には欠失はなく、de novo変異と考えられた。

## D．考察

DECIPHER databaseには似通った症例は数例登録されており、各登録施設と連携して臨床症状と染色体欠失との関連について解析した。その結果、女性におけるPLP1遺伝子周辺の微細欠失は、逆三角形の顔貌、重度精神発達遅滞、自傷行為などの行動異常などの共通した症状を示すことが明らかとなり、新規染色体微細欠失症候群と考えられた。欠失範囲の複数の遺伝子が脳で高発現しており、これらの遺伝子の欠失が関連していると考えられたが、男性におけるこの領域の欠失は胎生致死になると考えられ、そのことが先天性大脳白質形成不全症患者においてPLP1領域の欠失を示す例が少ない原因であると考えられた。

## E．結論

今回、診断未定多発奇形・発達遅滞を示す女性患者においてXq22の微細欠失を認め、他の複数の症例との比較から、新規染色体微細欠失症候群であると結論付けた。

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## G．知的所有権の取得状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

# Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書　籍

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| | | | | | |

# Ⅳ．研究成果の刊行物・別刷

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

# Pure Duplication of 19p13.3

**Aki Ishikawa,[1] Keisuke Enomoto,[1] Makiko Tominaga,[1] Toshiyuki Saito,[2] Jun-ichi Nagai,[2] Noritaka Furuya,[1] Kentaro Ueno,[3] Hideaki Ueda,[3] Mitsuo Masuno,[4] and Kenji Kurosawa[1,5]***

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Chromosomal abnormalities involving 19p13.3 have rarely been described in the published literature. Here, we report on a girl with a pure terminal duplication of 6.1 Mb on 19p13.3, caused by an unbalanced translocation der(19)t(10;19)(qter;p13.3)dn. Her phenotype included severe psychomotor developmental delay, skeletal malformations, and a distinctive facial appearance, similar to that of a patient previously reported by Lybaek et al. [Lybaek et al. (2009); Eur J Hum Genet 17:904–910]. These results suggest that a duplication of >3 Mb at the terminus of 19p13.3 might represent a distinct chromosomal syndrome.


**Key words:** 19p13.3 duplication; array CGH; developmental delay; subtelomere

**How to Cite this Article:**
Ishikawa A, Enomoto K, Tominaga M, Saito T, Nagai J, Furuya N, Ueno K, Ueda H, Masuno M, Kurosawa K. 2013. Pure duplication of 19p13.3.
Am J Med Genet Part A 161A:2300–2304.

## INTRODUCTION

Chromosome 19 is more gene-dense than any other human chromosome. Non-mosaic 19p trisomy is a rare chromosomal aberration, of which only 9 occurrences have been reported to date [Byrne et al., 1980; Salbert et al., 1992; Stratton et al., 1995; Andries et al., 2002; Puvabanditsin et al., 2009; Lybaek et al., 2009; Descartes et al., 2011; Siggberg et al., 2011; Lehman et al., 2012]. More specifically, pure and non-mosaic trisomy of 19p has been reported in only five of these patients [Stratton et al., 1995; Andries et al., 2002; Lybaek et al., 2009; Siggberg et al., 2011; Lehman et al., 2012].

Here, we report on a 3-year-old girl with pure terminal duplication of 19p13.3, confirmed using FISH and array CGH. She had multiple malformations, including a complex congenital heart defect, a distinctive facial appearance, and severe developmental delay. Taken together, our findings, along with a review of the literature, allow clarification of a more precise and comprehensive phenotype–genotype correlation for pure 19p duplication.

## CLINICAL REPORT

The proposita is the first child of healthy unrelated parents with unremarkable family history. At the time of delivery, the mother was 36 years old, and the father was 27 years old. The pregnancy was complicated by intrauterine growth retardation first noted at 27 weeks. The infant was delivered at 35 weeks of gestation by cesarean due to fetal distress. Her birth weight was 1,216 g; length, 36.5 cm; and occipitofrontal circumference (OFC), 28.0 cm. Her Apgar scores were 4 at 1 min, and 9 at 5 min. Because of her very low birth weight and respiratory failure, she was admitted to a neonatal intensive care unit. Initial physical examination showed a distinctive facial appearance with micrognathia, low-set ears, and a prominent occiput. An echocardiogram revealed a complete atrioventricular septal defect of Rastelli A type, severe pulmonary hypertension, and mitral valve dysplasia.

At the age of 8 months, catheter examination demonstrated that an operative procedure was not indicated for her heart defects; conservative treatment with beraprost sodium and bosentan hydrate, in addition to oxygen supplementation, was adopted for heart failure and severe pulmonary hypertension. From the age of 1 year and 8 months, sildenafil citrate was also added to her treatment. At this age, she had marked cardiac failure and had experienced several episodes of recurrent respiratory infection.

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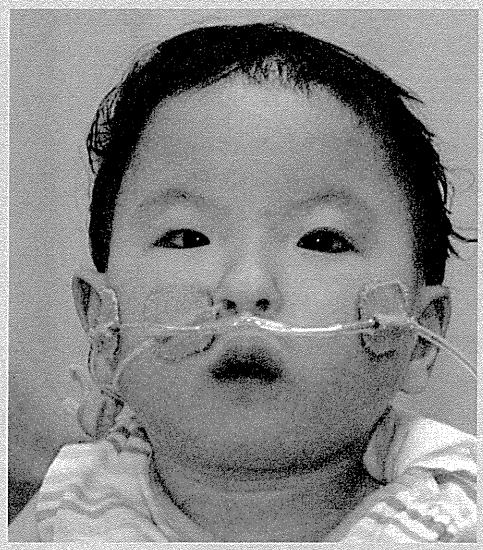

**FIG. 1. Patient at the age of 3 years, showing strabismus, short palpebral fissures, hypoplastic nasal alae, low-set ears, and microstomia.**

On examination at the age of 3 years, her weight was 7,680 g (−3.4 SD); height, 75 cm (−5.0 SD); and OFC, 42 cm (−4.0 SD) (Fig. 1). Her facial appearance showed strabismus, short and downslanting palpebral fissures, microcephaly, hypoplastic nasal alae, sparse scalp hair, and eyebrows, low-set ears, a short philtrum, protruding upper lip, and microstomia with micrognathia. Orthopedic examination showed kyphoscoliosis and dislocation of bilateral hip joints. Her development was severely delayed. She could roll over and required gavage feeding. Her heart failure progressed, and died at age 4 years. Postmortem examination revealed an ectopic left kidney in front of the vertebrae.

## MATERIALS AND METHODS

Written informed consent was obtained from the parents of the patient, and the study was performed in accordance with the Kanagawa Children's Medical Center Review Board and Ethics Committee.

An initial FISH analysis for patients with developmental delay/intellectual disability (DD/ID) and/or multiple congenital anomalies (MCA) was carried out using subtelomeric probes (Vysis, Downers Grove, IL) according to the standard protocol. Further FISH analysis for determining the breakpoint on 19p13.3 was carried out using bacterial artificial chromosome (BAC) clones that had been selected from the May 2004 (NCBI35/hg17). Human assembly of the UCSC Genome Browser (http://genome.ucsc.edu/). A centromeric probe specific for chromosome 10 was used to confirm chromosome 10. The BAC clones were labeled by nick translation according to the manufacturer's instructions (Vysis, Downers Grove, IL). Hybridization, post-hybridization washing, and counterstaining were performed according to standard procedures. Slides were analyzed using a completely motorized epifluorescence microscope (Leica DMRXA2; Leica Microsystems Imaging Solutions, Cambridge, UK) equipped with a CCD camera. Both the camera and microscope were controlled with Leica CW4000 M-FISH software [Yamamoto et al., 2009].

Array comparative genomic hybridization (array-CGH) was performed using the Agilent SurePrint G3 Human CGH Microarray Kit 8 × 60K (Agilent Technologies, Inc., Santa Clara, CA). The total genomic DNA of the patient was prepared using standard techniques. The results were analyzed using Agilent Genomic Workbench software. Only experiments having a derivative log ratio (DLR) spread value <0.30 were considered.

## RESULTS

The complete subtelomere probe set analysis detected an additional signal for 19pter on the terminal of the long arm in group C chromosomes in the patient. Based on the results of the G-banding patterns and FISH with a centromeric probe, the derivative chromosome was determined to be chromosome 10 (Fig. 2a,b). However, the 10qter probe signal was retained in the derivative chromosome (data not shown). To characterize the size of the deletion, we further applied FISH analysis using the BAC clones that mapped to the region. This revealed that the breakpoint was 6.1 Mb from 19pter (Table I). Subsequent array-CGH analysis revealed a 19p13.3 duplication of approximately 6.1 Mb (chr19: 327,273–6,106,229), which was consistent with the FISH results (Fig. 2c). No other genomic imbalances were identified on the array analysis. FISH analysis with relevant BAC clones indicated that the duplication was absent in both parents, and therefore had occurred de novo.

## DISCUSSION

Reports of abnormalities of the short arm chromosome 19 are rare; to date, only nine patients with non-mosaic duplication of 19p have been reported. Of these, four involved translocation of other chromosomes [Byrne et al., 1980; Salbert et al., 1992; Puvabanditsin et al., 2009; Descartes et al., 2011], and only five patients had a pure partial duplication of 19p [Stratton et al., 1995; Andries et al., 2002; Lybaek et al., 2009; Siggberg et al., 2011; Lehman et al., 2012] (Fig. 3., Table II). This report is, to our knowledge, only the second report of a pure terminal duplication of 19p13.3.

Array-CGH and FISH analysis refined the breakpoint at 6.1 Mb from 19pter. Three patients harboring a duplication of more than 1 Mb at 19p13.3 have been recorded on the DECIPHER database (https://decipher.sanger.ac.uk/), but no individual with a duplication of more than 3 Mb is recorded therein. Fourteen patients having a duplication of a fragment of 19p13.3 have been reported in the database of International Standards for Cytogenetic Arrays Consortium (ISCA). The phenotypical manifestations of these patients consist of multiple congenital abnormalities and seizures. However, the detailed phenotypic features of the patients were not available. Although the phenotype deriving from duplication of a limited region of 19pter is not always recognizable [Andries

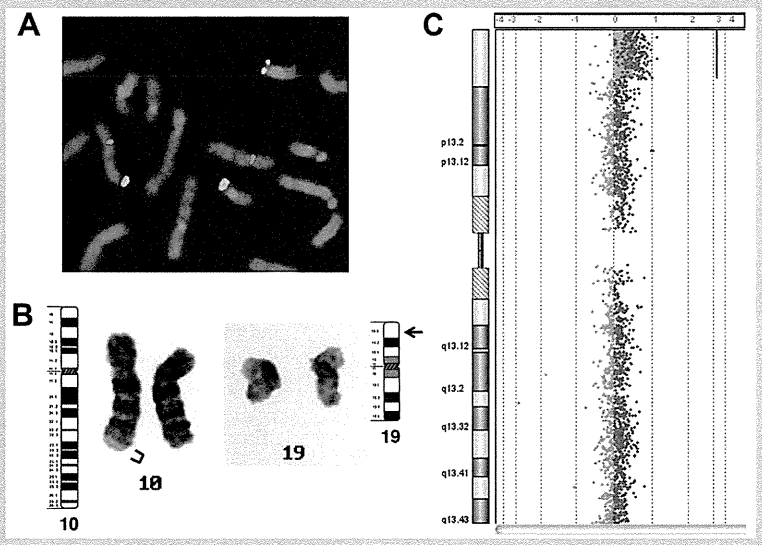


**FIG. 2. FISH and array-CGH characterization of 19p13.3 terminal duplication. A: FISH image showing an additional signal at 10qter. BAC probe RP11-43H17 from the duplicated region of 19p13.3 is labeled in green, and chromosome 10 centromeric probe (Vysis, CEP10) is labeled in red, as a control. B: G-banded metaphase chromosomes, showing der(10)t(10;19)(qter;p13.3). C: Array-CGH showing duplication of 19p13.3. The region extends to position 6,106,229 according to UCSC human genome assembly build 19.**

et al., 2002], the present case presented with severe psychomotor disability, no verbal language use, a distinctive facial appearance, and skeletal features including small hands and feet and bilateral hip dysplasia. These phenotypic features, especially the characteristic facial appearance, were also shared by the patient described by Lybaek et al. [2009]. The patient had a small mouth, short philtrum, full cheek, short palpebral fissures, and the extreme precocious puberty before the age of 5 months. They demonstrated that only about 25% of the duplicated 215 genes presented the overall expression pattern by more than 1.3-fold, and suggested no genes might explain the precocious puberty characterized in their patient. However, our present patient had no symptom of early puberty observed by the age of 4 years.

TABLE I. FISH Results Around the Breakpoint of the Translocation

| BAC clones | Position from 19pter[a] | FISH results |
|---|---|---|
| RP11-1051P16 | 3,421,215–3,617,048 | ×3 |
| RP11-43H17 | 4,318,718–4,491,568 | ×3 |
| RP11-348B12 | 4,960,407–5,144,570 | ×3 |
| RP11-294F21 | 5,854,144–6,041,711 | ×3 |
| RP11-576B17 | 6,172,183–6,249,454 | ×3 |
| RP11-114A7 | 6,199,888–6,359,433 | ×2 |
| RP11-30F17 | 6,351,112–6,519,252 | ×2 |
| RP11-459P1 | 6,396,557–6,544,479 | ×2 |
| RP11-526C20 | 6,450,800–6,626,432 | ×2 |
| RP11-222E10 | 6,560,463–6,759,394 | ×2 |
| RP11-441C15 | 7,891,868–8,086,997 | ×2 |

[a]Positions of the BAC clones were based on the May 2004 (NCBI35/hg17) Human Assembly of the UCSC Genome Browser (http://genome.ucsc.edu/).

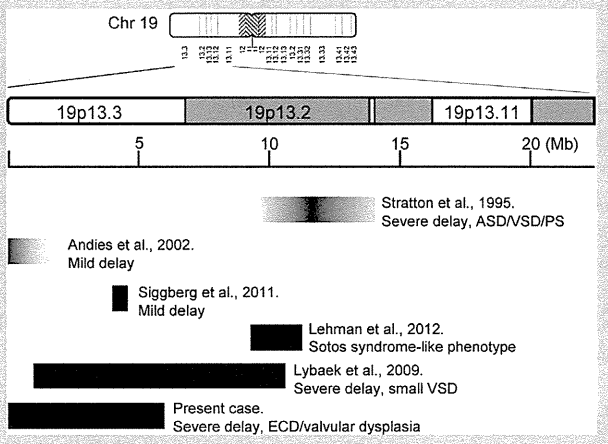


**FIG. 3. Schematic representation of the microduplication on 19p13.3. The dark horizontal bars indicate the range of the duplication in reported patients. The duplicated regions in the patients reported by Stratton et al. [1995] and Andries et al. [2002] were ascertained from the respective reports.**

TABLE II. Summary of Clinical Features in Five Individuals With Pure Microduplication at 19p13

| | Stratton et al. [1995] | Andries et al. [2002] | Siggberg et al. [2011] | Lehman et al. [2012] | Lybaek et al. [2009] | Present patient |
|---|---|---|---|---|---|---|
| Age, sex | 9 months, F | 20 months, F | 9 yrs, M | 1–74 yrs, M/F | 2 ½ yrs, F | 3yrs, F |
| Karyotype | dup(19)(p13.2p13.13) | der(14)t(14;19)(q32.3;p13.3) | dup(19)(p13.3p13.3) | dup(19)(p13.2p13.2) | ins(19)(q13.3p13.2-p13.3) | der(10)t(10;19)(qter;p13.3) |
| Duplication | p13.2–p13.13 | pter-p13.3 | p13.3, 0.81 Mb | p13.2. 1.9 Mb | p13.3–p13.2, 8.9 Mb | p13.3, 6.10 Mb |
| (from pter) | ? | ? | (3.927–4.471 Mb) | (9.109–11.068 Mb) | (1.4–10.3 Mb) | (–6.106 Mb) |
| Pattern | Interstitial | Terminal | Interstitial | Interstitial | Interstitial | Terminal |
| Gestational age | Term | 41 wks | Term | Term | 35 wks | 35 wks |
| Birth weight | 2,730 g | | 2,730 g | 4,550 g | 1,790 g | 1,216 g |
| Growth retardation | + | – | + | – | + | + Severe |
| Development | Delay | Mild delay | Mild delay | Mild delay | Severe delay | Severe delay |
| Cardiovascular | PS, ASD, VSD | — | — | — | small VSD | ECD, PH, valvular dysplasia |
| Others | Strabismus, nail hypoplasia | Sparse hair, low-set ears, short nose | Amblyopia | Sotos syndrome-like | Severe eating problem, congenital hip dysplasia | Strabismus, renal aplasia (L), vertebral defects, nail hypoplasia, dislocation of hip joint |

Thus, a duplication of >3 Mb of the terminal region of 19p13.3 might contribute to a more severe phenotype than do smaller duplications, and this phenotype might be characteristic of this chromosomal aberration.

Accurate assessment of the duplication size enabled us to evaluate the genes located within the duplicated region, which presumably contribute to the phenotypes. The duplicated region contains approximately 150 RefSeq genes and 130 OMIM genes, 18 of which have known disease associations. However, this case demonstrates that evaluation of the gene content of a chromosomal region is not sufficient to assess the pathogenicity of a gene duplication. Additional reports of individuals with this chromosomal aberration are required to demonstrate genotype–phenotype correlation in 19p duplication.

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RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

# Surgical Intervention for Esophageal Atresia in Patients With Trisomy 18

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Trisomy 18 is a common chromosomal aberration syndrome involving growth impairment, various malformations, poor prognosis, and severe developmental delay in survivors. Although esophageal atresia (EA) with tracheoesophageal fistula (TEF) is a potentially fatal complication that can only be rescued through surgical correction, no reports have addressed the efficacy of surgical intervention for EA in patients with trisomy 18. We reviewed detailed clinical information of 24 patients with trisomy 18 and EA who were admitted to two neonatal intensive care units in Japan and underwent intensive treatment including surgical interventions from 1982 to 2009. Nine patients underwent only palliative surgery, including six who underwent only gastrostomy or both gastrostomy and jejunostomy (Group 1) and three who underwent gastrostomy and TEF division (Group 2). The other 15 patients underwent radical surgery, including 10 who underwent single-stage esophago-esophagostomy with TEF division (Group 3) and five who underwent two-stage operation (gastrostomy followed by esophago-esophagostomy with TEF division) (Group 4). No intraoperative death or anesthetic complications were noted. Enteral feeding was accomplished in 17 patients, three of whom were fed orally. Three patients could be discharged home. The 1-year survival rate was 17%: 27% in those receiving radical surgery (Groups 3 and 4); 0% in those receiving palliative surgery (Groups 1 and 2). Most causes of death were related to cardiac complications. EA is not an absolute poor prognostic factor in patients with trisomy 18 undergoing radical surgery for EA and intensive cardiac management. 

**Key words:** trisomy 18; esophageal atresia; surgical intervention; neonatal intensive care; survival; causes of death

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## INTRODUCTION

Trisomy 18, first described by Edwards et al. [1960], is a common chromosomal aberration syndrome. Patients with the syndrome have prenatal-onset severe growth impairment, characteristic craniofacial features, various visceral and skeletal malformations, and a reduced lifespan; survivors have severe developmental delay [Carey, 2010]. The largest and most cited population-based study

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[Rasmussen et al., 2003] showed a 1-year survival rate of 5–8% and median survival time of 10–14.5 days. The major causes of death were reportedly apnea and withdrawal of treatment, and the presence of a congenital heart defect was not reported to be associated with early death [Embleton et al., 1996; Rasmussen et al., 2003].

Esophageal atresia (EA) with/without tracheoesophageal fistula (TEF) is a common esophageal malformation that occurs in between 1 in 3000–4000 live births. Currently, the best treatment option for EA with TEF in patients with no other severe malformations is primary single-staged correction comprising esophago-esophagostomy and TEF division. For patients with unstable respiratory and/or cardiovascular conditions, however, the procedure should be performed in steps [Pinheiro et al., 2012]. There have been three classification systems of preoperative risks regarding EA: the Waterston classification based on birth weight, associated anomalies, and pneumonia [Waterston et al., 1962]; the Montreal classification based on mechanical ventilation and associated congenital anomalies [Poenaru et al., 1993]; and the Spitz classification based on birth weight and cardiac anomalies [Spitz et al., 1994]. A recent report by Sugio et al. [2006] showed that birth weight might no longer be a risk factor. Patients with EA were reported to have other abnormalities: cardiovascular complications (23%), musculoskeletal malformations (18%), and chromosomal aberrations (5.5%). Patients with life-threatening anomalies, including Potter syndrome, cerebral hypoplasia, and chromosomal abnormalities such as trisomy 13 or 18, as well as infants with totally uncorrectable major cardiac defects or grade IV intraventricular hemorrhage, were recommended to undergo nonoperative management [Pinheiro et al., 2012]. The accurate frequency of EA in trisomy 18 has not been determined by systematic investigation, and only an institution-based study from Japan demonstrated that a total of 33% (8/24) patients with trisomy 18 had EA, representing the most common non-cardiac visceral malformation [Kosho et al., 2006]. Although EA with TEF is a potentially fatal complication that can only be rescued through surgical correction, no reports have addressed the efficacy of surgical intervention for EA in patients with trisomy 18.

We herein describe the detailed clinical information of patients with trisomy 18 and EA who were admitted to two Japanese institutions that provided intensive treatment including surgical correction for EA in these patients.

## MATERIALS AND METHODS

### Patients

Patient data were collected from two institutions in Japan. Nagano Children's Hospital (NCH), established in 1993, is a tertiary hospital for sick children in Nagano Prefecture, which reports roughly 20,000 births per year. Since the obstetric department was established in 2000, pregnant women whose fetuses were found to have severe abnormalities by ultrasonography have also been referred for further evaluation, genetic counseling, and delivery. In the neonatal intensive care unit of this hospital, patients with this syndrome have been managed under the principle of providing intensive treatment based on careful discussion with the parents. The management comprises resuscitation including intratracheal intubation, appropriate respiratory support, establishment of enteral nutrition including corrective and palliative surgery for gastrointestinal malformation, and pharmacological treatment for congenital heart defects. This management was demonstrated to improve survival, with a 1-year survival rate of 25% and median survival time of 152.5 days. The common underlying factors associated with death were congenital heart defects and heart failure (96%) followed by pulmonary hypertension (78%), and the common final modes of death were sudden cardiac or cardiopulmonary arrest (26%) and progressive pulmonary hypertension-related events (26%) [Kosho et al., 2006]. The surgical strategy for EA in patients with trisomy 18 has been to perform gastrostomy soon after birth, followed by a second surgery after stabilization of the general condition (esophago-esophagostomy and TEF division from 1993 to 2003; TEF division from 2003).

The Central Hospital of Aichi Human Service Center (CHAHSC), established in 1970, is a tertiary hospital for sick children and handicapped children/adults covering the northern part of Aichi prefecture and the southern part of Gifu prefecture, which report roughly 70,000 births per year. The management principle of this hospital has been to perform intensive treatment including surgery for every patient, whether he/she has a severe disorder and/or handicap, if he/she needs the treatment or surgery for longer survival and better quality of life. The surgical strategy for EA in patients with trisomy 18 has been to perform esophago-esophagostomy with TEF division as a one-stage operation, whereas a two-stage operation comprising gastrostomy and jejunostomy followed by esophago-esophagostomy was planned in the early period.

A total of 27 patients with karyotypically confirmed full trisomy 18 and EA were admitted to the neonatal intensive care units of NCH from April 1993 to March 2008 and CHAHSC from April 1982 to March 2009. Two patients with A-type EA and one patient who died of uncontrollable respiratory failure before surgery were excluded. The other 24 patients (9 boys, 15 girls; Patients 1, 3, 5, 6, 7, 9, 20–24 from NCH, Patients 2, 4, 8, 10–19 from CHAHSC) with C-type EA who underwent surgery were included in this study (Table I).

### Methods

From the medical records of NCH and CHAHSC, we collected detailed clinical data about the surgical methods and courses of EA in the 24 patients including eight who were described in our previous study [Kosho et al., 2006]. In addition, their perinatal conditions and interventions, other medical complications and treatments, and prognosis including survival and discharge were reviewed. We classified the patients into four groups (Table I): Group 1 (Patients 1–6) underwent gastrostomy with/without jejunostomy; Group 2 (Patients 7–9) underwent gastrostomy and TEF division; Group 3 (Patients 10–19) underwent esophago-esophagostomy with TEF division as one operation; and Group 4 (Patients 20–24) underwent gastrostomy followed by esophago-esophagostomy with TEF division.

## TABLE I. Clinical Information of Patients With Trisomy 18 Undergoing Surgery for Esophageal Atresia

| | | Perinatal conditions | | | | | | | Complications | | | | Intervention | | | | Prognosis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | Surgery for esophageal atresia | | Crdiovascular | Respiratory | | | | | |
| Patient | Sex | Gestational age (weeks/days) | Birth weight (g) | Apgar score (1/5 min) | Prenatal diagnosis by amniocentesis | Polyhydramnios | Cesarean section | Resuscitation by intubation | Congenital heart defects | Respiratory complications | Gastrointestinal complications | Urogenital system, Seizure | Methods (age [days] at surgery) | Complications | Cardiac intervention | IMV/extubation (day) or TS | Enteral/oral feeding | Discharge (days) | Survival (days) | Underlying factors associated with death | Final cause of death |
| Group 1: Gastrostomy+Jejunostomy | | | | | | | | | | | | | | | | | | | | | |
| 1 | M | 31/4 | 1,017 | 2/2 | − | + | + | + | AVSD, DORV | TA, DE, LH | | HU, RD | GS (0) | | DO, NG | +/− | − | | 1 | CHD, HF, TA, LH, RsF | RsF |
| 2 | M | 34/1 | 1,420 | | − | | − | + | VSD, PDA | | | HK, IH | GS+JS (1) | | D | +/− | + | | 9 | CHD, HF | SCA |
| 3 | F | 39/3 | 1,956 | 2/4 | − | + | + | − | ASD, VSD, PDA | RTI | | | GS (0) | Bleeding | D, DO | +/− | − | | 12 | CHD, PH, HF | Aspiration pneumonia |
| 4 | F | 35/1 | 1,464 | −/5 | − | + | + | + | VSD | PnT | GER | HN | GS+JS (1) | | None | +/− | + | | 20 | CHD, PH, Hemorrhagic tendency | PHE, RsF |
| 5 | M | 36/0 | 1,220 | 4/7 | − | + | + | + | VSD, PDA | | Microileum | HN | GS (0) | | D, DG, DO | +/− | − | | 41 | CHD, PH, HF, Malnutrition | HF, PHE |
| 6 | M | 41/5 | 1,990 | 1/5 | + | + | − | + | PDA, ASD | | | Sz | GS (0) | | D | +/− | − | | 133 | CHD, PH, HF | HF |
| Group 2: Gastrostomy+Tracheoesophageal fistula division | | | | | | | | | | | | | | | | | | | | | |
| 7 | M | 34/5 | 1,515 | 1/6 | − | + | + | + | VSD, PDA | | | | GS (2), TEFD (29) | ChT | D, DG, DO | +/− | + | | 47 | CHD, PH, HF | HF |
| 8 | F | 35/6 | 1,152 | 7/9 | + | + | + | − | VSD, ASD, PDA | | | Sz | GS+TEFD (5) | ChT | D | +/− | + | | 106 | CHD, CLD, PH | HF |
| 9 | F | 35/2 | 1,412 | 5/9 | + | + | + | − | AVSD, PDA | Tracheomalacia | | | GS (0), TEFD (29) | | D, NG, PGI2 | +/− | + | | 172 | CHD, PH, HF | HF |
| Group 3: Esophago-esophagostomy+Tracheoesophageal fistula division | | | | | | | | | | | | | | | | | | | | | |
| 10 | F | 37/4 | 1,776 | −/5 | − | + | − | + | ASD, VSD, PDA | | | | EES+TEFD (1) | | DO | +/− | − | | 2 | CHD, PPHN, HF | SCA |
| 11 | F | 36/0 | 1,510 | −/5 | − | | + | + | CoA, VSD, MS, AS | | | PK, RnF | EES+TEFD (3) | | D, PGE1, DO | +/− | + | | 17 | CHD, HF, PK | HF, RnF |
| 12 | F | 39/4 | 1,840 | 5/8 | − | + | + | − | VSD, PS | RTI | GER | | GS+EES+TEFD (1) | | D, DG, DO | +/− | + | | 17 | CHD, RTI, PHE | HF, PHE |
| 13 | M | 33/5 | 1,364 | 8/8 | − | + | + | − | ASD, VSD, PDA | RTI | | HN, RnF | EES+TEFD (0) | | D, DO, PDA ligation | +/− | − | | 18 | CHD, HF | HF, RsF |
| 14 | F | 41/1 | 2,320 | −/9 | − | | − | − | VSD, TR | | | RnF | EES+TEFD (2) | | D, DO | +/− | − | | 23 | CHD, PH, HF, RsF | HF |
| 15 | M | 35/0 | 938 | | − | + | − | + | VSD, PH | | | | EES+TEFD (0) | | D, DG | +/− | + | | 27 | CHD, PH | SCA |
| 16 | F | 40/0 | 1,670 | 7/8 | − | + | + | − | VSD, ASD, PDA | RTI | GER | HK | EES+TEFD (1) | | D, DG | +/− | + | | 70 | CHD, PH, RTI | HF |
| 17 | M | 35/1 | 1,560 | 1/4 | − | + | − | + | VSD, PDA | RTI | Enteritis Hypertrophic pyloric stenosis | | EES+TEFD (2) | | D, DO | +/− | + | | 202 | CHD, PH, CLD | HF |
| 18 | F | 36/0 | 1,488 | 5/9 | − | | + | + | VSD, ASD, PS | | | Sz | EES+TEFD (1) | | D | +/− | +/+ | | 236 | CHD, PH | HF |
| 19 | F | 37/1 | 1,759 | 4/7 | − | + | + | − | ASD, VSD | | | | EES+TEFD (1) | PnT | D, DG | +/+ (7) | +/+ | + (73) | 694 | CHD, PH | HF |
| Group 4: Gastrostomy followed by Esophago-esophagostomy + Tracheoesophageal fistula division | | | | | | | | | | | | | | | | | | | | | |
| 20 | M | 35/4 | 1,310 | 7/8 | − | + | + | + | VSD, ASD | | | Sz | GS (0), EES+TEFD (14) | Mediastinitis | D, DO | +/− | + | | 32 | CHD, PH, HF, RsF, Mediastinitis | HF, RsF |
| 21 | F | 36/4 | 1,804 | 1/1 | − | + | − | + | VSD, PDA | | GER | Sz | GS (1), EES+TEFD (93) | Atelectasis | D, DO, NG | +/+ (125) | + | + (137) | 210 | CHD, CLD, PH | SCA |
| 22 | M | 37/4 | 1,747 | 2/3 | − | + | + | − | VSD | RTI | AM | HN, Sz | GS (0), EES+TEFD (3) | | D, DO, NG | +/TS | + | | 518 | CHD, PH | PH crisis |
| 23 | F | 36/1 | 1,422 | 8/9 | − | + | − | − | PDA, VSD (closed) | RTI | GER, AM | Sz | GS (0), EES+TEFD (17) | | D | +/− | + | | 580 | RnF, Malnutrition | RnF |
| 24 | F | 35/1 | 1,420 | 5/8 | − | + | + | + | PA, VSD, PDA | | | VUR | GS (1), EES+TEFD (6) | TEF recanalization | D, DG, PGE1 | +/TS | +/+ | + (947) | 1,786 | CHD, PH, HF, RsF | Tube trouble |

M, male; F, female; AM, anorectal malformation; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular defect; ChT, chylothorax; CHD, congenital heart defects; CLD, chronic lung disease; CoA, coarctation of aorta; D, diuretics; DE, diaphragmatic eventration; DG, digoxin; DO, dopamine and/or dobutamine; DORV, double outlet right ventricular; EA, esophageal atresia; EES, esophago-esophagostomy; GER, gastroesophageal reflux; GS, gastrostomy; HF, heart failure; HK, horseshoe kidney; HN, hydronephrosis; HU, hydroureter; IH, inguinal hernia; IMV, intermittent mandatory ventilation; JS, jejunostomy; LH, lung hypoplasia; MS, mitral valve stenosis; NG, nitroglycerin; PA, pulmonary atresia; PDA, patent ductus arteriosus; PGE1, prostaglandin E1; PGI2, prostaglandin I2; PH, pulmonary hypertension; PHE, pulmonary hemorrhage; PK, polycystic kidney; PnT, pneumothorax; PPHN, persistent pulmonary hypertension of the newborn; PS, pulmonary stenosis; RD, renal dysplasia; RnF, renal failure; RsF, respiratory failure; RTI, respiratory truct infection; SCA, sudden cardiac or cardiopulmonary arrest; Sz, Seizure; TA, tracheoatresia; TEFD, tracheoesophageal fistura division; TOF, tetralogy of fallot; TR, tricuspid valve regurgitaion; TS, tracheostomy; VSD, ventricular septal defect; VUR, vesicoureteral reflux.