Constitutional chromosomal abnormalities are an important cause of miscarriage, infertility, congenital anomalies, and mental retardation in humans.³ Constitutional chromosomal abnormalities include numerical chromosome aberrations that cause aneuploidy and structural chromosome aberrations such as translocations, inversions, deletions, and duplications. The frequency of structural chromosomal abnormalities has been estimated as 0.25% in live-born infants.² Chromosomal polymorphisms of constitutive heterochromatin regions of chromosomes 1, 9, 16, and the Y chromosome have been reported.¹ The pericentric inversion of the heterochromatic region of chromosome 9 [inv(9)], inv(9)(p11q13), or inv(9)(p12q13), is the most common pericentric inversion found in the human karyotype.⁴

Because the inv(9) has been found in - 3.57% of human samples without apparent phenotypic consequences, inv(9) is considered to be a structural chromosomal abnormality.
variant in the general population. In this study we re-evaluated cases with congenital anomalies associated with \textit{de novo} inv(9).

**MATERIALS AND METHODS**

**Patients**

For the clinical and cytogenetic analyses, we studied 431 neonates with congenital anomalies at the Pediatric Clinic in Ajou University Hospital between 2004 and 2008. A detailed clinical investigation was performed in eight patients with a pericentric inversion, inv(9)(p11q13).

**Cytogenetic analysis**

Peripheral blood samples and the clinical data were obtained from 431 patients and 19 parents of affected individuals, with informed consent provided from all parents of patients according to the institutional review board of the Ajou University Hospital. Cytogenetic analysis was performed on G-bands by trypsin using Giemsa (GTG)-banded metaphase spreads prepared from PHA-stimulated peripheral blood lymphocytes. Chromosome analyses were performed on 20 metaphases for each sample with a resolution of 450 bands. The constitutional karyotypes were described in accordance with the ISCN.

**RESULTS**

We investigated the clinical profiles of 431 newborn cases with congenital anomalies including: age, gender, history of consanguinity, maternal and paternal factors, family history, pedigree, and associated diseases. The clinical characteristics of the patients are listed in Table 1. To confirm the existence of chromosomal aberrations in the patients, we carried out cytogenetic studies on all patients. As shown in Table 2, among the 431 neonates, chromosomal aberrations were found in 60 patients (13.9%). Numerical abnormalities were found in 34 patients (7.9%). The nume-

| Table 1. Clinical Characteristics of 431 Korean Neonates with Congenital Anomalies |
|-------------------------------------------------|-----------------|
| Clinical manifestations                          | Number of patients |
| Total                                           | 431             |
| Abnormal karyotype on amniocentesis             | 4               |
| Multiple spontaneous abortions in the mother    | 1               |
| Hematological disease                           | 2               |
| Seizures                                        | 7               |
| Deafness                                        | 2               |
| Hypotonia                                       | 6               |
| Typical morphology and suspected syndromes      | 34              |
| Edward syndrome                                 | 1               |
| Cri-du chat syndrome                            | 2               |
| Down syndrome                                   | 31              |
| Anomalies of the central nervous system          | 26              |
| Abnormal facial morphology                      | 87              |
| Abnormalities of the skin                       | 5               |
| Anomalies of the gastrointestinal tract          | 70              |
| Congenital heart disease                        | 22              |
| Abnormal genitalia                              | 17              |
| Anomalies of renal system                       | 15              |
| Skeletal anomalies                              | 48              |
| Multiple anomalies                              | 7               |
| Congenital tumor                                | 2               |
| Simian crease                                   | 18              |
| Single umbilical artery                         | 38              |
| Muscular dystrophy                              | 2               |
| Hydrops fetalis                                 | 9               |
| Intrauterine growth restriction                 | 9               |
rical abnormalities included Down syndrome among 28 patients (6.5%), Edward syndrome, Klinefelter syndrome, 47,XXX, and mosaicism. Structural abnormalities were found in 26 patients (6.0%). Inversions, translocations, deletions, addition, insertion, ring chromosome, 16qh+, and 21ps+ were found. Two inversions, inv(8)(q13q24.1) and inv(9)(p11q13), were detected.

We focused further study on the pericentric inversion of chromosome 9, inv(9)(p11q13), because it was the most common type of structural abnormality (8 cases) identified in this study. No other chromosomal abnormalities were found in these patients with inv(9)(p11q13), and representative karyotypes were obtained in the parents of the affected patients, indicating that all cases with inv(9)(p11q13) were de novo.

The patients with inv(9)(p11q13) had various dysmorphic features and/or congenital anomalies including: polydactyly, club foot, microtia, deafness, asymmetric face, giant Meckel’s diverticulum, duodenal diaphragm, small bowel malrotation, pulmonary stenosis, atrial septal defect, tricuspid regurgitation, cardiomyopathy, arrhythmia, intrauterine growth restriction, and oligohydramnios (Table 3) (Fig. 2). The patient with polydactyly had a thumb duplication on standard X-ray (Fig. 2A). In the patient with a giant Meckel’s diverticulum, barium filled the large cystic mass at the distal part of the ileum (Fig. 2B). In the patient

Table 2. Chromosome Abnormalities Identified by Karyotypes of the Patients

| Type of chromosome aberration | Number of patients | %   |
|-------------------------------|--------------------|-----|
| Total                         | 60                 | 13.9|
| Numerical aberrations         | 34                 | 7.9 |
| Down syndrome                 | 28                 | 6.5 |
| Edward syndrome               | 1                  | 0.2 |
| Klinefelter syndrome           | 1                  | 0.2 |
| 47,XXX                        | 1                  | 0.2 |
| Mosaicism                     | 3                  | 0.7 |
| Structural aberrations        | 26                 | 6.0 |
| Inversion                     | 9                  | 2.1 |
| inv(9)(p11q13)                | 8                  | 1.9 |
| inv(8)(q13q24.1)              | 1                  | 0.2 |
| Translocation                 | 3                  | 0.7 |
| Deletion                      | 4                  | 0.9 |
| Addition                      | 4                  | 0.9 |
| Insertion                     | 1                  | 0.2 |
| Ring chromosome               | 1                  | 0.2 |
| Increased length of the heterochromatin, 16qh+ | 3 | 0.7 |
| Increased length of the satellite, 21ps+ | 1 | 0.2 |

Fig. 1. GTG-banded karyotypes of the lymphocytes from patients with pericentric inversion of chromosome 9. The constitutional karyotypes of cases 3 and 8 were 46,XY, inv(9)(p11q13) and 46,XX, inv(9)(p11q13), respectively. No other chromosomal aberrations were detected in either case. GTG, G-bands by trypsin using Giemsa.

Fig. 2. Congenital anomalies associated with inv(9)(p11q13) (Case 3 and Case 8). The patient with polydactyly had a thumb duplication on standard X-ray (Fig. 2A). In the patient with a giant Meckel’s diverticulum, barium filled the large cystic mass at the distal part of the ileum (Fig. 2B).
with the duodenal diaphragm and small bowel malrotation, a dilated duodenal bulb and obstructed lower portion of the duodenum was observed on an upper gastrointestinal study (Fig. 2C). In the patient with hypertrophic cardiomyopathy, atrial septal defect, arrhythmia, club foot, and oligohydramnios, and cardiomegaly were identified (Fig. 2D). In the patient with unilateral microtia and an asymmetric face, the external auditory canal of the right ear was absent on three-dimensional reconstruction images of the computed tomography (Fig. 2E). Brain stem-evoked audiometry responses were tested in all patients. One patient (case 7) was found to have severe hearing difficulty in both ears, and in the patient with microtia, the affected ear was non-responsive to stimuli. We followed these patients for 6 to 32 months and performed developmental assessments with the Bayley and social maturity scales. All patients showed normal progress in motor, language, and social development.

**DISCUSSION**

Chromosomal inversion is a common structural rearrange-
inv(9) is one of the most common structural balanced chromosomal variations. The incidence of inv(9) has been found to differ among ethnic groups and the overall incidence has been estimated to be 3.57% in various populations by antenatal cytogenetic analysis and peripheral blood karyotype analysis.14 A previous study reported that in 6,250 referred antenatal cases of four major ethnic groups, the incidence of inv(9) was highest in the Black population (3.57%), slightly above average in Hispanics (2.42%), and relatively low in Whites (0.73%) and Asians (0.26%).15 In another study of Asian populations, the overall incidences of inv(9) were estimated to be 1.2% in antenatal groups in Singapore and 1.95% among normal and patient populations in Japan.16 In this study, inv(9) was observed in 1.9% of the total referred newborn cases (n = 431) and this data is similar to that of a previous report in Korea (1.7%).17 As shown in the previous study, the incidence of inv(9) in fetuses was significantly higher in females than males; our data also showed more females (7:1).

In this study, we detected various abnormalities in eight patients with inv(9), including polydactyly, club foot, microtia, deafness, asymmetric face, giant Meckel’s diverticulum, duodenal diaphragm, small bowel malrotation, pulmonary stenosis, atrial septal defect, cardiomyopathy, arrhythmia, and intrauterine growth restriction (Table 3)(Fig. 2). There were no commonly shared clinical features; however, polydactyly was found in cases 1 and 2, gastrointestinal abnormalities in cases 3 and 4, atrial septal defect and oligohydramnios in cases 5 and 6, and unilateral microtia in cases 7 and 8. In the literature, a few reports have shown that inv(9) was detected in patients with various congenital anomalies such as a dysmorphic face, congenital cataract, blindness, deafness, cleft palate, congenital heart anomalies, hydronephrosis, amenorrhea, short stature, short toes, microcephaly, and urogenital anomalies.15-17 There were no overlapping clinical phenotypes. This indicates that inv(9) was not pathogenic.

Recently complex chromosomal rearrangements, with more than two chromosomal breaks, have been identified more frequently than it had been before the human genome project era. This was supported by a higher prevalence of inv(9) in the Down syndrome population in comparison to the normal population.18 A higher prevalence of inv(9) has been reported in couples with habitual abortion and a history of more than two spontaneous first trimester abortions,19 aborted fetuses,20 and among the schizophrenia population.21 Although no specific or common manifestations have been identified in these populations, a few studies have reported that inv(9) is sometimes associated with various clinical phenotypes related to fertilization,15 fetal development,19 morphogenesis,11,12 growth,14 acute leukemia,20 and ovarian cancer.21

The cytogenetic analysis of the parents revealed that all cases were de novo heterozygous inv(9)(p11q13). Karyotypes of peripheral blood lymphocytes from the patients demonstrated that no other chromosomal aberrations except inv(9)(p11q13) were present (Fig. 1). However, there is the possibility of microdeletions or duplications that could not be detected by the karyotypes in these patients. Unlike the inherited inv(9) found in normal populations, de novo pericentric inversions would be expected to have other cryptic genomic abnormalities. This may explain why de novo inv(9) is associated with various clinical features.

ACKNOWLEDGEMENTS

This work was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (A050234) and the National Research Foundation of Korea Grant funded by the Korean Government (331-2006-1-E00029).

REFERENCES

1. McFadden DE, Friedman JM. Chromosome abnormalities in human beings. Mutat Res 1997;396:129-40.
2. Jacobs PA, Hassold TJ. Chromosome abnormalities: origin and etiology in abortions and livebirths. In: Vogel F, Sperling K, editors. Berlin: Human Genetics, Springer; 1987. p.233-44.
3. Hsu LY, Benn PA, Tannenbaum HL, Perlis TE, Carlson AD. Chromosomal polymorphisms of 1, 9, 16, and Y in 4 major ethnic groups: a large prenatal study. Am J Med Genet 1987;26:95-101.
4. Kaiser P. Pericentric inversions. Problems and significance for clinical genetics. Hum Genet 1984;68:1-47.
5. Teo SH, Tan M, Knight L, Yeo SH, Ng I. Pericentric inversion 9—incidence and clinical significance. Ann Acad Med Singapore 1995;24:302-4.
6. Yamada K. Population studies of INV(9) chromosomes in 4,300 Japanese: incidence, sex difference and clinical significance. Jpn J Hum Genet 1992;37:293-301.
7. Kim JJ, Rhee HS, Chung YT, Park SY, Choi SK. Prenatal detection of de novo inversion of chromosome 9 with duplicated heterochromatic region and postnatal follow-up. Exp Mol Med 1999;
31:134-6.
8. ISCN. An International System for Human Cytogenetic Nomenclature, 2009. In: Shaffer LG, Slovak ML, Campbell LJ. Basel: Karger; 2009.
9. Starke H, Seidel J, Henn W, Reichardt S, Volleth M, Stumm M, et al. Homologous sequences at human chromosome 9 bands p12 and q13-21.1 are involved in different patterns of pericentric rearrangements. Eur J Hum Genet 2002;10:790-800.
10. Kim SS, Jung SC, Kim HJ, Moon HR, Lee JS. Chromosome abnormalities in a referred population for suspected chromosomal aberrations: a report of 4117 cases. J Korean Med Sci 1999;14:373-6.
11. Rao BV, Kerketta L, Korgaonkar S, Ghosh K. Pericentric inversion of chromosome 9[inv(9)(p12q13)]: Its association with genetic diseases. Indian J Hum Genet 2006;12:129-32.
12. Scarinci R, Anichini C, Vivarelli R, Berardi R, Pucci L, Rossa L, et al. [Correlation of the clinical phenotype with a pericentric inversion of chromosome 9.] Boll Soc Ital Biol Sper 1992;68:175-81.
13. Baltaci V, Ors R, Kaya M, Balci S. A case associated with Walker-Warburg syndrome phenotype and homozygous pericentric inversion 9: coincidental finding or aetiological factor? Acta Paediatr 1999;88:579-83.
14. Stanojević M, Stipoljev F, Koprcina B, Kurjak A. Oculo-auriculo-vertebral (Goldenhar) spectrum associated with pericentric inversion 9: coincidental findings or etiologic factor? J Craniofac Genet Dev Biol 2000;20:150-4.
15. Salihu HM, Boos R, Tchuenguem G, Schmidt W. Prenatal diagnosis of translocation and a single pericentric inversion 9: the value of fetal ultrasound. J Obstet Gynaecol 2001;21:474-7.
16. Serra A, Brahe C, Millington-Ward A, Neri G, Tedeschi B, Tassone F, et al. Pericentric inversion of chromosome 9: prevalence in 300 Down syndrome families and molecular studies of nondisjunction. Am J Med Genet Suppl 1990;7:162-8.
17. Demirhan O, Taştemir D. Chromosome aberrations in a schizophrenia population. Schizophr Res 2003;65:1-7.
18. Uehara S, Akai Y, Takeyama Y, Takabayashi T, Okamura K, Yajima A. Pericentric inversion of chromosome 9 in prenatal diagnosis and infertility. Tohoku J Exp Med 1992;166:417-27.
19. Kim JW, Lee JY,HWang JW, Hong KE. Behavioral and developmental characteristics of children with inversion of chromosome 9 in Korea: a preliminary study. Child Psychiatry Hum Dev 2005;35:347-57.
20. Keung YK, Knovich MA, Powell BL, Buss DH, Pettenati M. Constitutional pericentric inversion of chromosome 9 and acute leukemia. Cancer Genet Cytogenet 2003;145:82-5.
21. Yasuhara T, Okamoto A, Kitagawa T, Nikaido T, Yoshimura T, Yanaihara N, et al. FGF7-like gene is associated with pericentric inversion of chromosome 9, and FGF7 is involved in the development of ovarian cancer. Int J Onco 2005;26:1209-16.