Original Article | DOI 10.3349/ymj.2010.51.5.775 pISSN: 0513-5796, eISSN: 1976-2437 | Yonsei Med J 51(5):775-780, 2010 | YMJ

De Novo Pericentric Inversion of Chromosome 9 in Congenital Anomaly

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Received: November 12, 2009
Revised: December 30, 2009
Accepted: December 30, 2009
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· The authors have no financial conflicts of interest.

Purpose: The pericentric inversion of chromosome 9 is one of the most common structural balanced chromosomal variations and has been found in both normal populations and patients with various abnormal phenotypes and diseases. The aim of this study was to re-evaluate the clinical impact of inv(9)(p11q13). **Materials and Methods:** We studied the karyotypes of 431 neonates with congenital anomalies at the Pediatric Clinic in Ajou University Hospital between 2004 and 2008 and retrospectively reviewed their clinical data. **Results:** Chromosomal aberrations were detected in 60 patients (13.9%). The most common type of structural abnormality was inv(9)(p11q13), found in eight patients. Clinical investigation revealed that all eight cases with inv(9)(p11q13) had various congenital anomalies including: polydactyly, club foot, microtia, deafness, asymmetric face, giant Meckel's diverticulum, duodenal diaphragm, small bowel malrotation, pulmonary stenosis, cardiomyopathy, arrhythmia, and intrauterine growth restriction. The cytogenetic analysis of parents showed that all of the cases were *de novo* heterozygous inv(9)(p11q13). **Conclusion:** Since our results indicate that the incidence of inv(9)(p11q13) in patients with congenital anomalies was not significantly different from the normal population, inv(9)(p11q13) does not appear to be pathogenic with regard to the congenital anomalies. Some other, to date unknown, causes of the anomalies remain to be identified.

Key Words: Chromosomal variation, congenital anomaly, dysmorphic feature, inv(9), pericentric inversion

INTRODUCTION

Constitutional chromosomal abnormalities are an important cause of miscarriage, infertility, congenital anomalies, and mental retardation in humans.[1] 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.[3] 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

variant in the general population.[3,5-7] In this study we re-evaluated cases with congenital anomalies associated with *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.[8]

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

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

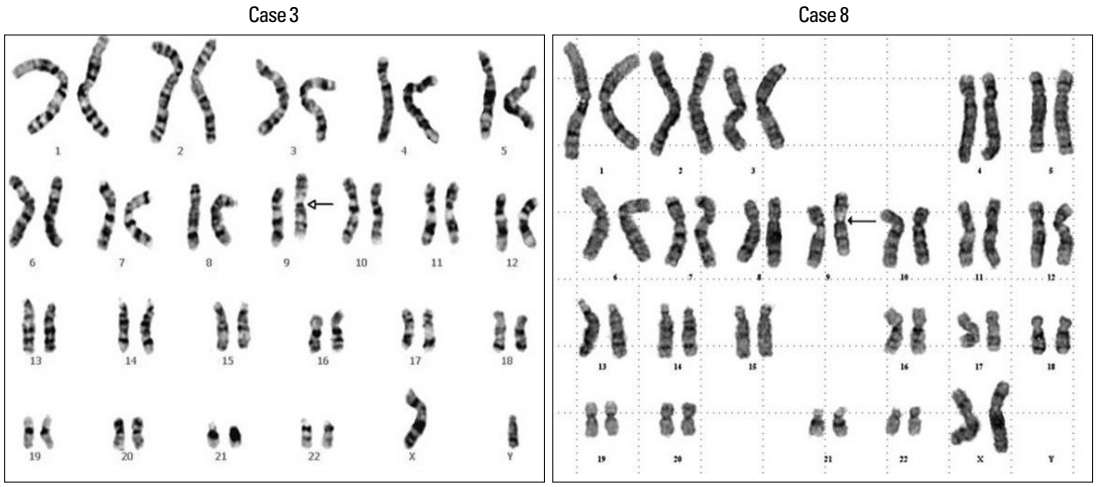

Fig. 1. GTG-banded karyotypes of the lymphocytes from patients with pericentric inversion of chromosome 9. The constitutional karyotypes of cases 3 and 8 were 46,XY, inv(9)(p11q13) and 46,XX, inv(9)(p11q13), respectively. No other chromosomal aberrations were detected in either case. GTG, G-bands by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

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 represen-Normal 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

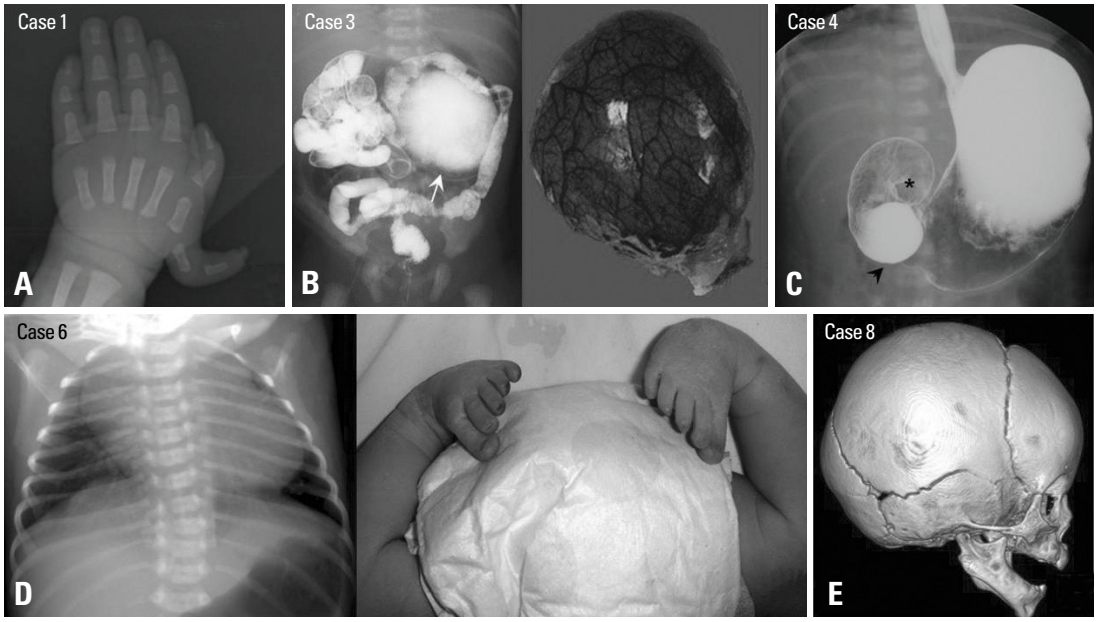

Fig. 2. Clinical and radiological features of patients with *de novo* inv(9)(p11q13). (A) Thumb duplication is seen on standard X-ray of one female newborn. (B) Barium filled the large cystic mass of the distal part of the ileum (arrow). Pathology specimen demonstrates the size of the giant Meckel's diverticulum. (C) Dilated duodenal bulb (arrowhead) and the obstructed lower portion of the duodenum (asterisk) is seen on the upper gastrointestinal study of one male newborn with a duodenal diaphragm and small bowel malrotation. (D) Cardiomegaly is seen on the standard chest X-ray and a prominent club foot is also present in one female newborn with congenital arrhythmia. (E) External auditory canal of the right ear is absent on three-dimensional reconstruction images of the computed tomography in one female newborn with unilateral microtia.

Table 3. Clinical Features of the Patients with *de novo* inv(9)(p11q13)

Case	Sex	GA (weeks)	Bwt (g)	Maternal age	Paternal age	Clinical features
Case 1	F	40.2	3,150	27	33	Polydactyly
Case 2	F	39.0	2,400	34	29	Polydactyly
Case 3	M	36.1	2,660	29	29	Giant Meckels's diverticulum
Case 4	F	38.1	2,670	30	29	Duodenal diaphragm, malrotation of small bowels
Case 5	F	30.1	1,170	32	36	Pulmonary stenosis, tricuspid regurgitation, atrial septal defect intrauterine growth restriction, oligohydrmanios
Case 6	F	39.2	2,920	39	42	Hypertrophic cardiomyopathy, atrial septal defect, arrhythmia, club foot, oligohydramnios
Case 7	F	39	2,300	30	39	Unilateral microtia, deafness
Case 8	F	38.6	3,100	32	37	Unilateral microtia, asymmetric face

GA, gestational ages; Bwt, birth weight.

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-

ment that originates from two breaks on the same chromosome followed by reinsertion of the 180° rotated broken fragment. Human chromosome 9 is highly susceptible to structural chromosomal rearrangement and various types of pericentric inversions have been reported including: inv (9)(p11q13), inv(9)(p11q12), inv(9)(p11q21), inv(9) (p12q13), inv(9)(p13q13), and inv(9)(p13q21); the variable breakpoints are preferentially located in the 9p12 or 9q13-21.1 regions.[9] Among them, inv(9)(p11q13) and inv(9) (p12q13) cannot be distinguished on karyotypes and 'inv(9)' represents these two karyotypes.

The 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.[3-6] 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%).[3] 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.[5,6] 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%).[10] As shown in the previous study, the incidence of inv(9) in fetuses was significantly higher in females than males;[7] 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.[11-15] 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 expected 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.[16] 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,[6] aborted fetuses,[6] and among the schizophrenia population.[17] 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,[18] fetal development,[19] morphogenesis,[11,12] growth,[15] 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).

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