Case Report

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Prenatal diagnosis of interchromosomal insertion of Y chromosome heterochromatin in a family

Bom-Yi Lee[1], Ju-Yeon Park[1], Yeon-Woo Lee[1], Ah-Rum Oh[1], Shin-Young Lee[1], So-Yeon Park[1], Hyun-Mee Ryu[1,2], and Si-Won Lee[2,*]

[1]Laboratory of Medical Genetics, Cheil General Hospital and Women's Healthcare Center, Seoul, Korea

[2]Department of Obstetrics and Gynecology, Cheil General Hospital and Women's Healthcare Center, Dankook University College of Medicine, Seoul, Korea

Interchromosomal insertion of Y chromosome heterochromatin in an autosome was identified in a fetus and a family. A fetal karyotype was analyzed as 46,XX,dup(7)(?q22q21.1) in a referred amniocentesis at 16 weeks of gestation for advanced maternal age. In the familial karyotype analyses for identification of der(7), the mother, the first daughter and the maternal grandmother showed the same der(7) as the fetus's. CBG-banding was positive at 7q22 region of der(7) that indicated inserted material was originated from heterochromatin. The origin of heterochromatic insertion region in der(7) of the fetus and the mother was found in Yq12 region by fluorescent *in situ* hybridization with a DYZ1 probe. In the specific analysis of Y chromosomal heterochromatic region of ins(7;Y) of the mother, 15 sequence tagged sites from Yp11.3 region including *SRY* to Yq11.223 region was not detected. Final karyotypes of the mother, the first daughter and the maternal grandmother were reported as 46,XX,der(7)ins(7;Y)(q21.3;q12q12). All female carriers of ins(7;Y) in the family showed normal phenotype and the mother and the maternal grandmother were fertile. A healthy girl was born at term. We report a rare case of familial interchromosomal insertion of Y chromosome heterochromatin detected only in female family members with normal phenotype that was diagnosed prenatally.

Key words: Insertion, Y chromosome, Heterochromatin, Prenatal diagnosis.

Introduction

The incidence of balanced translocations between the Y chromosome and an autosome in the general population is approximately 1 in 2,000 [1]. Rearrangement of the Y chromosome involving autosomes are known to interfere X-Y sex vesicle formation during the pachytene stage of meiosis resulting in spermatogenic arrest and infertility in the male [2]. Most of Y-autosome translocations occur between the Y chromosome and the short arm of acrocentric chromosomes of D or G groups, predominantly chromosome 15 or 22 [2,3]. The Y chromosome and non-acrocentric translocations are uncommon.

Breakpoint at the chromosome Y usually occurs at Yq11.2 or Yq12 heterochromatin region [4]. About half of the Y chromosome is comprised of the variable region of heterochromatin. The testis-determining gene, *SRY*, pseudoautosomal regions, and azoospermia factor regions are on the Y euchromatic region [2]. Constitutive heterochromatin regions such as chromosome 1qh, 9qh, 16qh, and Yq12 are known to be transcriptionally and genetically inactive during the cell cycle [2].

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*Corresponding author: Si-Won Lee, M.D., Ph.D.
Department of Obstetrics and Gynecology, Cheil General Hospital and Women's Healthcare Center, Dankook University College of Medicine, 17 Seoae-ro 1-gil, Jung-gu, Seoul 04619, Korea.
Tel: +82-2-2000-7682, Fax: +82-2-2278-4574, E-mail: c1loveya@naver.com

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Insertions are one type of translocation and rare chromosomal rearrangement event. The incidence of simple one-way interchromosomal insertion is estimated to be 1 in 80,000 in standard karyotype analysis [5]. In all types of chromosomal rearrangements, genetically balanced rearrangements without deleterious effect at breakpoints would show normal clinical phenotypes.

We report a familial prenatal case of Y chromosome heterochromatin insertion into the long arm of autosome 7 confirmed by conventional cytogenetic analysis and fluorescent *in situ* hybridization (FISH). Carriers of an ins(7;Y) in the family are all females in three generations with normal phenotypes. This study was approved by the Ethics Committee of Cheil General Hospital and Women's Health Care Center (#CGH-IRB-2016-45) and patients' consent was obtained.

Case

A healthy 40-year-old Korean woman (gravida 2, para 1) (II-2 in Fig. 1) was referred for amniocentesis at 16 weeks of gestation for advanced maternal age. Amniotic fluid alpha-fetoprotein levels were 1.18 MoM (normal ranges 0-2.5 MoM). Her pregnancy was unremarkable and fetal ultrasound findings were normal. Chromosome analysis of cultured amniocytes was analyzed at least 30 metaphases according to standard cytogenetic protocols in a laboratory. Chromosome 7 of the fetus (III-2 in Fig. 1) showed an unbalanced duplication at 7q22 region (Figs. 2A and B). The fetal karyotype was reported as 46,XX,dup(7)(?q22q21.1).

To confirm origin of fetal der(7), high resolution chromosome preparations for the parents were examined with GTL-, CBG-, and RBG-banding techniques according to the previous report [6]. The mother (II-2 in Fig. 1) was confirmed to be a carrier of der(7) which is the same as the fetus's by GTL-, CBG-, and RBG-banding (Figs. 2E-G). To identify duplication of 7q22, FISH was performed using a probe of a Williams-Beuren ELN (7q11) spectrum orange signal with internal control of 7q22 spectrum green signal for chromosome 7 (Kreatech Diagnostics, Amsterdam, The Netherlands) according to the manufacturer's instructions. FISH analysis showed no duplication or deletion signals on both probe regions. However, DAPI-counter stain was positive at 7q22 region suggesting an insertion of heterochromatin material (data not shown). CBG-banding also showed positively at fetal der(7) at 7q22 (Fig. 2C). We performed another FISH analysis to identify characteristics of heterochromatic region of der(7) for the fetus and the mother using Yq12 chromosome-specific probes (Vysis CEP Y [DYZ1] Sat III Spectrum Green; Abbott Mo-

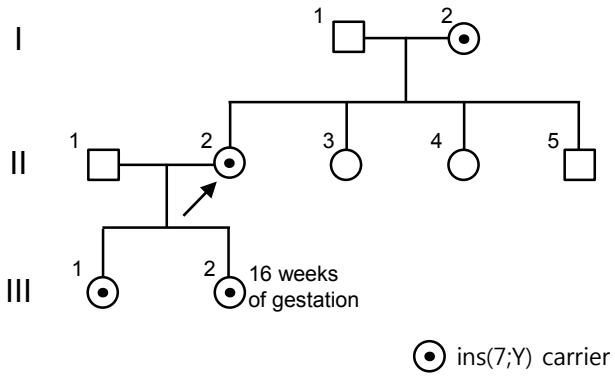

Fig. 1. Pedigree for inheritance of ins(7;Y). The arrows represents a pregnant woman who is referred for amniocentesis and carries a fetus with ins(7;Y) (II-2). Four female family members (I-2, II-2, III-1, and III-2) carry ins(7;Y) that has Yq12 heterochromatin insertion on chromosome 7q21.3.

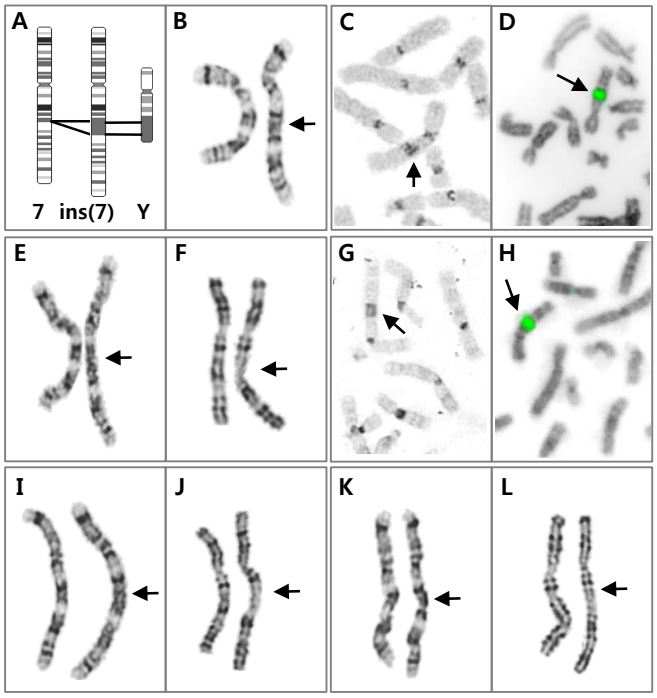

Fig. 2. Partial karyotypes of ins(7;Y) carriers in a family. (A) Ideograms of normal chromosome 7 (left), ins(7;Y) (middle), and normal Y chromosome (right). (B) GTL-banded chromosome 7 and ins(7;Y) (arrow) of the fetus (III-2). (C) CTG-banded ins(7;Y) (arrow) of the fetus. (D) Fluorescent *in situ* hybridization (FISH) with a DYZ1 probe (Spectrum Green) for Yq12 heterochromatin on ins(7;Y) (arrow) of the fetus. (E) GTL-banded chromosome 7 and ins(7;Y) (arrow) of mother (II-2). (F) RBG-banded chromosome 7 and ins(7;Y) (arrow) of the mother. (G) CTG-banded ins(7;Y) (arrow) of the mother. (H) FISH with a DYZ1 probe (Spectrum Green) for Yq12 heterochromatin on ins(7;Y) (arrow) of the mother. (I) GTL-banded chromosome 7 and ins(7;Y) (arrow) of the first daughter (III-1). (J) RBG-banded chromosome 7 and ins(7;Y) (arrow) of the first daughter. (K) GTL-banded chromosome 7 and ins(7;Y) (arrow) of the maternal grandmother (I-2). (L) RBG-banded chromosome 7 and ins(7;Y) (arrow) of the maternal grandmother.

lecular Inc., Des Plaines, IL, USA). Yq12 specific probe signal was detected at 7q21.3 region of both fetus and mother (Figs. 2D and H).

For the specific analysis of Y chromosomal heterochromatic region of ins(7;Y), multiplex PCR was performed for maternal DNA isolated from peripheral blood using 16 sequence tagged site (STS) markers according to the protocol of our previous study [6] ; 15 STS for Yp11.3 (sY14, *SRY*), Yq11.21 (sY86), Yq11.21 (sY84), Yq11.222 (sY124), Yq11.222 (sY127), Yq11.223 (sY130), Yq11.223 (sY129), Yq11.223 (sY134), Yq11.223 (sY147), Yq11.223 (sY242), Yq11.223 (sY254), Yq11.223 (sY255), Yq11.223 (*SPGY1*), Yq11.223 (sY157), Yq11.223 (sY158) and one STS for Xp21.3 (*ZFX*). We were unable to detect 15 STS markers located at the Y chromosome in maternal DNA (Fig. 3). After combined analysis of the results of cytogenetic and molecular genetic tests, the mother's karyotype was reported as 46,XX,der(7)ins(7;Y)(q21.3;q12q12).

Additionally peripheral blood samples for chromosome studies were collected from the first daughter (III-1 in Fig. 1) and maternal families (I-1, I-2, II-3, II-4, and II-5 in Fig. 1) at 20.3 weeks of gestation. Twenty metaphases of high resolution were analyzed to identify der(7) by GTL-banding. CBG- and RBG-banding according to the previous report [6]. The results of the analysis were as follows. Ten-year-old first daughter (III-1) and 64-year-old maternal grandmother (I-2) demonstrated the same der(7) as the fetus's (Figs. 2I-L). They are all healthy and phenotypically normal. Genetic counseling was done at 21.6 weeks of gestation and parents opted to continue the pregnancy. A girl was delivered at 39.2 weeks of gestation with a birth weight of 3,300 g. She had a normal appearance and nonspecific findings in the physical and neurologic examinations and no additional abnormalities were noted at six months of age.

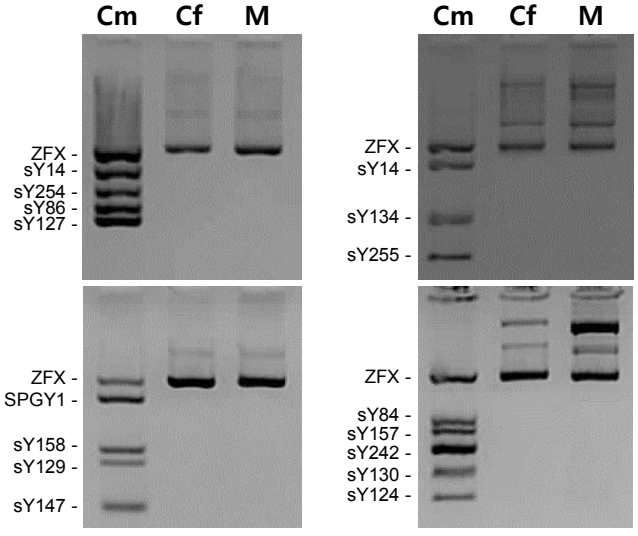

Fig. 3. Multiplex polymerase chain reaction analysis with sequence tagged site (STS) markers. Except for the *ZFX* marker located on the chromosome Xp21.3, all of the STS markers on the chromosome Y are not detected in the mother (II-2).
Cm, male control; Cf, female control; M, mother.

Discussion

Unbalanced chromosomal rearrangements detected in prenatal diagnosis always have increased a risk of structural anomaly in a fetus and recurrence at next pregnancy. To our knowledge, the present case is the first case with interchromosomal insertion of Y chromosome heterochromatin at the chromosome 7 as 46,XX,der(7)ins(7;Y)(q21.3;q12q12) detected in prenatal diagnosis and in a family. Carriers with unbalanced rearrangement of Yq12 region were all females in three generations with normal phenotype and adult females were fertile and had no abortion history.

There were a few case reports showing a type of interchromosomal insertion of heterochromatin including female carriers running in a family. Harmless C-band positive insertion from autosome or Y chromosome at 11q23.2 was detected in karyotype analyses of the maternal grandfather, the mother, and the boy in three generations. Adult carriers were all healthy; however, the boy showed severe developmental delay and anal stenosis. They assumed the possibility of disruptive effect of breakpoint which allele was inherited from the father who was carrier of autosomal recessive genetic disorder at 11q23 [7]. In another family through three generations, the grandmother, the father, and the boy carried der(11)ins(11;Y)(q24;q12q12) and they were also all healthy and normal appearance [8]. In addition, although this was not a type of interchromosomal insertion, there was a case report in France showing normal phenotypic two females with 46,XX,der(1)t(Y;1)(q12;p36) which might have been inherited through seven generations regardless of gender in a family [9].

Insertion is a type of translocation and is a rare chromosomal rearrangement event. The prevalence of simple one-way interchromosomal insertion resulting in live birth is estimated to be 1 in 80,000 in standard karyotype analysis [5]. In addition, interchromosomal insertion of Yq12 is very rare. Female carriers carrying Yq12 region due to Y; acrocentric chromosomes have been reported that 1/2,000 or 1/3,000 females [10,11]. Most common (70%) type of Yq12 rearrangement is involved with acrocentric chromosomes 15 and 22 [4]. This has shown the same incidence rate regardless of gender and is stable once formed [2].

However, there was a case of imbalanced genetic transmis-

sion from a fertile father with 45,X,t(Y;15)(q12;p11) to a son 46,XX,t(Y;15)(q12;p11) with *SRY*, who showed azoospermia [12]. Structural abnormalities of the Y chromosome have been observed in 10% to 20% of men with non-obstructive azoospermic infertility [13]. Despite having balanced translocation, translocation of the sex chromosome Y and autosomes except for acrocentric chromosomes would interrupt sex vesicle formation and would induce impaired X-Y bivalent in pachytene stage and subsequent arrest of spermatogenesis leading to azoospermia and infertility in 80% of the cases [4].

Most frequent breakpoints of Y chromosome in those cases occur at Yq11 or Yq12. In addition to the breakpoint Yq11.2 due to AZF disruption, genetically inert heterochromatic region of Yq12 is also detected in azoospermic males [8]. Constitutive heterochromatin such as chromosome 1, 9, 16 and Yqh is transcriptionally and genetically inactive during interphase, replicated in the synthesis late S phase of the cell cycle, rich in highly repetitive DNA and no active genes, and never elongate or decondense [14]. Otherwise, facultative heterochrmain could change state of condensation and could have active genes such as female inactive X chromosomes. The size of heterochromatin regions in humans could be variable and it is stained darkly than euchromatin region [14]. The Y chromosome of 57 Mbp in total size is composed of about half of variable region of heterochromatin (Yq12), the testis-determining gene, *SRY* (Yp11.3), pseudoautosomal region PAR1 (Yp11) and PAR2 (Yq12) containing chromosome X homologous loci, and azoospermia factor regions, AZFa, b, and c (Yq11.1-11.2) [15].

The first chromosomal rearrangement event in this family might have occurred due to a homogeneous sequences resulting in non-allelic homologous recombination between the chromosome 7 and Yq12 regions. The der(Y) derived in reciprocal rearrangement with der(7) inherited from the first male ancestor might be lost in a female gamete. In the following generation, recombination and unbalanced translocation may have occurred with other chromosomal heterochromatic regions, particularly in male gametes which would be lead to fertility problems. Otherwise, ins(7) would be inherited stably without gene disruption in the breakpoint.

As a limitation, extra molecular genetic analyses for an identification of precise breakpoint of the chromosome 7 were not available in a regular prenatal cytogenetic diagnosis because of insufficient prenatal specimen. In recent years, high-resolution methods, including multiplex ligation-dependent probe amplification, array-comparative genomic hybridization, and next-generation sequencing allowed identification of a number of individuals with cryptic chromosomal rearrangement such as micro-deletions/duplication. Therefore, we also emphasis the role of standard cytogenetic analysis, special bandings, and FISH analysis for the identification of chromosomal rearrangements in routine prenatal and postnatal diagnosis regardless of genomic dosage. It could allow more sufficient genetic counseling for the family to prevent recurrence in a family.

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