



Prenatal diagnosis of an unbalanced translocation between chromosome Y and chromosome 15 in a female fetus

Dongsook Lee^{1,2}, Heeju Park¹, Sanha Kwak¹, Soomin Lee¹, Sanghee Go¹, Sohyun Park¹, Sukyung Jo¹, Kichul Kim¹, Seungwan Lee², and Doyeong Hwang^{1,*}

¹Research Center of Fertility & Genetics, Hamchoon Women's Clinic, Seoul, Korea

²Department of Health and Environmental Science, Korea University, Seoul, Korea

We report the prenatal diagnosis of an unbalanced translocation between chromosome Y and chromosome 15 in a female fetus. Cytogenetic analysis of parental chromosomes revealed that the mother had a normal 46,XX karyotype, whereas the father exhibited a 46,XY,der(15)t(Y;15) karyotype. We performed cytogenetic analysis of the father's family as a result of the father and confirmed the same karyotype in his mother and brother. Fluorescence *in situ* hybridization and quantitative fluorescent-polymerase chain reaction analysis identified the breakpoint and demonstrated the absence of the SRY gene in female members. Thus, the proband inherited this translocation from the father and grandmother. This makes the prediction of the fetal phenotype possible through assessing the grandmother. Therefore, we suggest that conventional cytogenetic and molecular cytogenetic methods, in combination with family history, provide informative results for prenatal diagnosis and prenatal genetic counseling.

Key words: Prenatal diagnosis, der(15)t(Y;15)(q12;p11), Sex chromosome aberrations, Fluorescence *in situ* hybridization, Quantitative fluorescent PCR.

Introduction

Translocations involving the Y chromosome and an autosomal chromosome are very rare, occurring in approximately 1/2,000 of the general population. The most frequent translocation of this type occurs between the heterochromatin of the long arm of chromosome Y and the short arm of chromosome 15 [1,2]. This may be the result of a frequent sequence homology based association of the 15p and Yq heterochromatin, during the pachytene stage of male meiosis [3]. The breakpoints are

frequently located within the chromosome 15p11–15p13 and Yq11.23–Yq12 regions. These types of translocations are equally found in male and female patients, and carriers of t(Y;15) usually have a normal phenotype [2,4].

We report the prenatal diagnosis of an unbalanced translocation between chromosome Y and chromosome 15 in a female fetus, inherited from a paternal carrier. Molecular cytogenetic methods were used to cytogenetically characterize the der(15) translocation, and family history was helpful in prenatal counseling.

Received: 16 November 2016, Revised: 4 December 2016, Accepted: 4 December 2016, Published: 31 December 2016

*Corresponding author: Doyeong Hwang, Ph.D.

Research Center of Fertility & Genetics, Hamchoon Women's Clinic, 10 Seochojungang-ro 8-gil, Seocho-gu, Seoul 06643, Korea.

Tel: +82-2-522-0123, Fax: +82-2-522-2388, E-mail: doyhwang@hamchoon.com

Conflict of interest: The authors declare that they do not have any conflicts of interest.

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

© Copyright 2016 by the Korean Society of Medical Genetics

www.e-kjgm.org

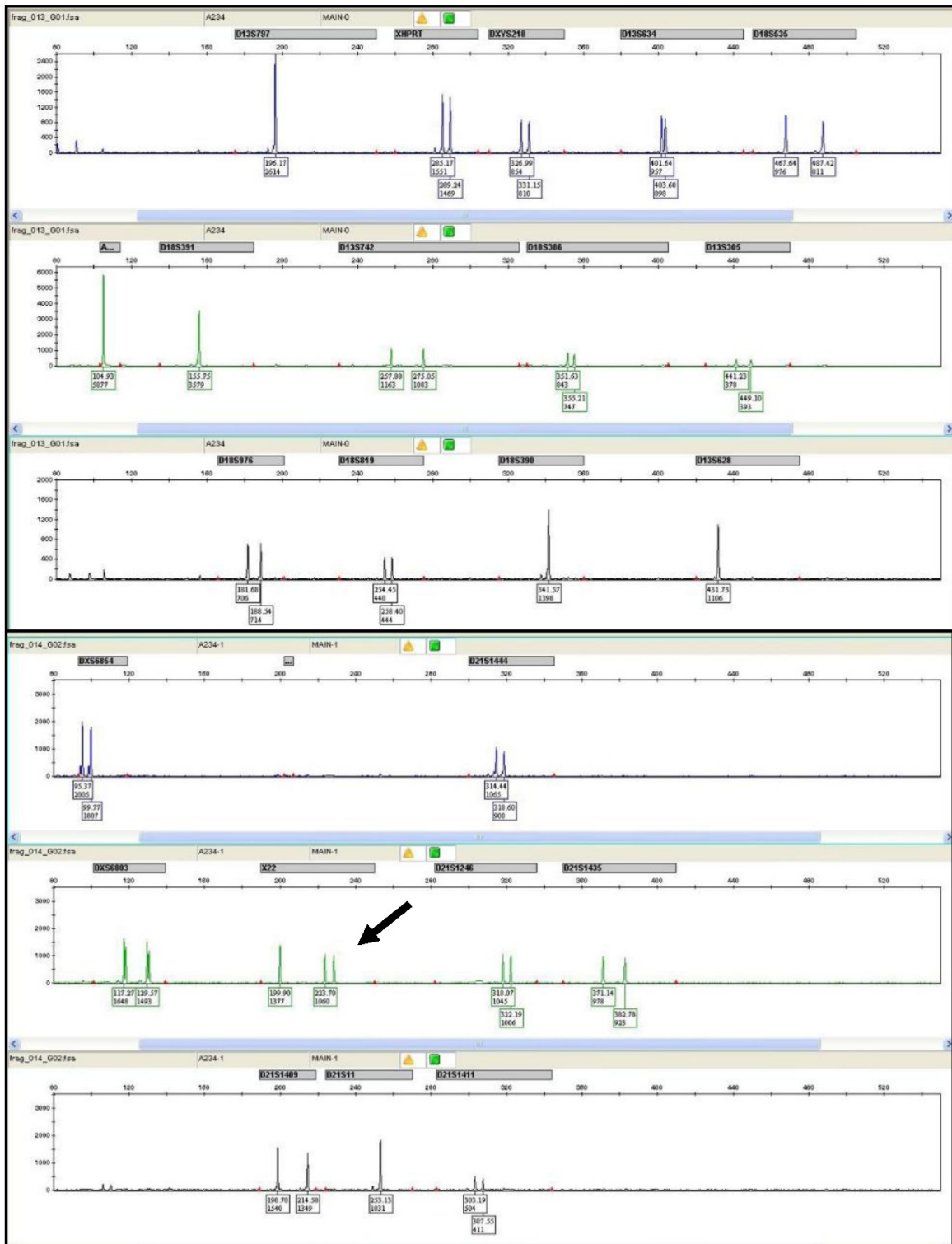


Fig. 1. Electrophoregram of prenatal diagnostic quantitative fluorescent polymerase chain reaction (QF-PCR; Cybergene AB, Stockholm, Sweden). A total of five short tandem repeats from chromosome 13 (D13S256, D13S303, D13618, D13S631, D13S634), five from chromosome 18 (D18S386, D18S391, D18S535, D18S858, D18S976), six from chromosome 21 (D21S11, D21S1411, D21S1412, D21S1413, D21S1435, D21S1444), three from chromosome X (DXS996, DXS1283, P39) and two from the pseudoautosomal regions PAR1 and PAR2 (X22 and DXYS218) were included. *AMXY* and *SRY* were also included. Prenatal testing results, revealed that chromosomes 13, 18 and 21 were normal. *AMXY* and chromosome X markers indicated that the proband was *SRY* negative and female, respectively. One (X22, arrow) of the pseudoautosomal regions PAR1 and PAR2 (X22 and DXYS218) was abnormal. The grandmother's results were the same as those of the proband (not shown).

Case

A 40-year-old pregnant woman was referred for amniotic fluid sampling at 16 weeks and three days due to advanced maternal age. Quantitative fluorescent polymerase chain reaction (QF-PCR) was performed in uncultured amniocytes using a set of short tandem repeat markers for chromosomes 13, 18, 21, X, and Y (Cybergene AB, Stockholm, Sweden). QF-PCR results revealed one abnormal pattern (X22) representing two pseudoautosomal regions PAR1 and PAR2 (X22 and DXYS218) (Fig. 1).

Cytogenetic analysis results showed the presence of additional material on the p-arm of one chromosome 15 (III-1 in Fig. 2). The karyotypes of the proband's parents were examined to determine if this atypical chromosome 15 was inherited or occurred *de novo*. Cytogenetics results revealed that the proband's father had the same der(15) chromosome, while the proband's mother exhibited a normal karyotype. Dark G-banding observed on the p-arm structure of the der(15) showed that it was likely to correspond to heterochromatin (II-1 in Fig. 2).

We characterized the der(15) chromosome using fluorescence *in situ* hybridization (FISH) analysis. FISH analysis was performed by hybridizing combined probes targeting chromosome Y and centromeric 15 (CEP15) (Fig. 3). Finally, the proband's karyotype was interpreted as 46,XX,der(15)t(Y;15)(q12;p11) pat. To predict the phenotype of the proband, we conducted a cytogenetic analysis of the father's family. This analysis revealed

that the father's mother and brother carried the same der(15) chromosome (I-2 and II-3 in Fig. 2). QF-PCR results of the proband's grandmother (I-2 in Fig. 2) revealed the same pattern for the X22 marker as the proband (not shown). Therefore, through the grandmother we can predict the phenotype of the fetus for purposes of genetic counseling.

Discussion

In prenatal diagnosis, prediction of phenotypes caused by

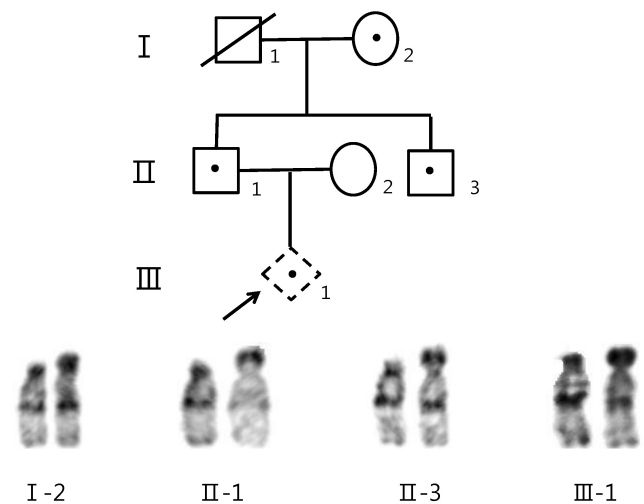


Fig. 2. Family pedigrees and cytogenetic characterization of the der(15) translocation.

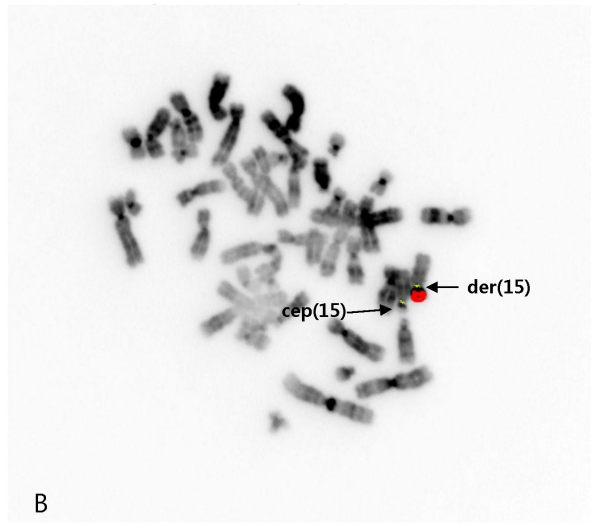
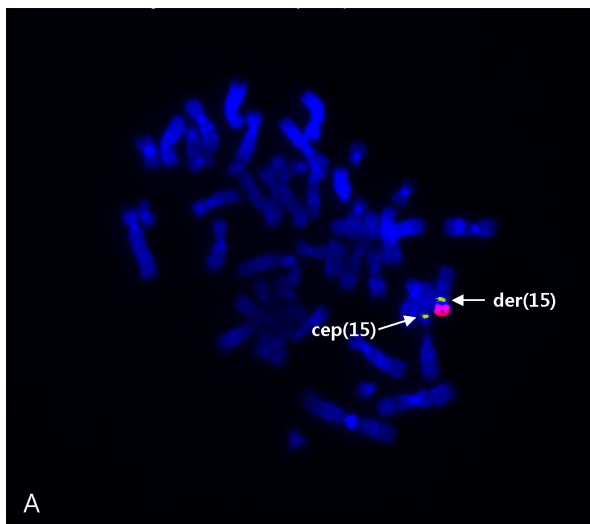


Fig. 3. Fluorescence *in situ* hybridization results showed the presence of two chromosome 15 positive regions (arrows). The derived chromosome 15 of cultured amniocytes from III-1 contains Yq12 (I-2 was same results. Not shown). The probe for chromosome Yq12 (DYZ1, satellite III; Vysis, Chicago, IL, USA) is labelled in red. The probe, for chromosome 15 CEP (D15Z1; Vysis) is labelled in green. (A) Background 4',6-diamidino-2-phenylindole (DAPI) image, (B) inverted DAPI image.

unknown chromosome fragments or translocations is big dilemma. Here, the unknown chromosome fragment identified during prenatal diagnosis was very confusing. However, QF-PCR results suggested that the abnormal chromosome related structural abnormality was found. QF-PCR is a very powerful tool for prenatal diagnosis of the most common aneuploidies. However, the detection of a trisomic pattern in only one marker, is more problematic. In such cases, parents should be tested to identify the presence of a duplication, and to rule out the possibility of partial trisomy. In the case of X22, heterochromatic Y chromosome material has already been described [5,6].

In this case, the translocation origin and breakpoints were determined through FISH using CEP 15, and Y specific probes. Our results demonstrate that standard karyotyping, in combination with FISH, is useful for the detection of rare chromosomal rearrangements. Some cases with Prader-Willi syndrome (PWS) exhibit translocations involving chromosome 15 with deletion of PWS regions [2,7-10]. However, by using CEP 15 (Fig. 3), we confirmed that the breakpoint in this case does not include the PWS region.

Accurate identification of der(15) chromosomal content during prenatal cytogenetic analysis may facilitate the prediction of the fetal phenotype. Therefore, characterizing the der(15) chromosome using FISH is recommended. The der(15) t(Y;15)(q12;p13) translocation identified in the present work is the most common form of Y-autosome translocation. While this karyotype appears unbalanced, examination of the family history and identification of the same chromosome in the paternal grandmother (I-1 in Fig. 2), reveals that the phenotype of the proband is predicted to be normal female.

Therefore we suggest that conventional cytogenetic methods, combined with molecular cytogenetic methods and family history, are very informative for prenatal diagnosis and prenatal genetic counseling.

References

1. Onrat ST, Söylemez Z, Elmas M. 46,XX, der(15),t(Y;15)(q12;p11) karyotype in an azoospermic male. *Indian J Hum Genet* 2012;18:241-5.
2. Chen Y, Chen G, Lian Y, Gao X, Huang J, Qiao J. A normal birth following preimplantation genetic diagnosis by FISH determination in the carriers of der(15)t(Y;15)(Yq12;15p11) translocations: two case reports. *J Assist Reprod Genet* 2007;24:483-8.
3. Alitalo T, Tiihonen J, Hakola P, de la Chapelle A. Molecular characterization of a Y;15 translocation segregating in a family. *Hum Genet* 1988;79:29-35.
4. Chen PY, Yen JH, Cheng CF, Chen PC, Li YS, Li TY, et al. Prenatal diagnosis of the maternal derivative chromosome der(15)t(Y;15)(q12;p13) in a dizygotic twin pregnancy. *Tzu Chi Med J* 2016;28:176-9.
5. Badenas C, Rodríguez-Revenga L, Morales C, Mediano C, Plaja A, Pérez-Iribarne MM, et al. Assessment of QF-PCR as the first approach in prenatal diagnosis. *J Mol Diagn* 2010;12:828-34.
6. Cirigliano V, Voglino G, Ordoñez E, Marongiu A, Paz Cañadas M, Ejarque M, et al. Rapid prenatal diagnosis of common chromosome aneuploidies by QF-PCR, results of 9 years of clinical experience. *Prenat Diagn* 2009;29:40-9.
7. Distèche CM, Brown L, Saal H, Friedman C, Thuline HC, Hoar DI, et al. Molecular detection of a translocation (Y;15) in a 45,X male. *Hum Genet* 1986;74:372-7.
8. Gal A, Weber B, Neri G, Serra A, Müller U, Schempp W, et al. A 45,X male with Y-specific DNA translocated onto chromosome 15. *Am J Hum Genet* 1987;40:477-88.
9. Morel F, Duguépéroux I, McElreavey K, Le Bris MJ, Herry A, Parent P, et al. Transmission of an unbalanced (Y;1) translocation in Brittany, France. *J Med Genet* 2002;39:e52.
10. Hoshi N, Fujita M, Mikuni M, Fujino T, Okuyama K, Handa Y, et al. Seminoma in a postmenopausal woman with a Y;15 translocation in peripheral blood lymphocytes and a t(Y;15)/45,X Turner mosaic pattern in skin fibroblasts. *J Med Genet* 1998;35:852-6.