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Abnormal reproductive history associated with aberrant chromosomal structure: two cases

Hailong Zhai[1], Zhongjuan Li[1*], Haibo Zhu[2], Jianping Deng[2], Hongliang Wang[3]

[1]Hubei Polytechnic University, Medical School, Huangshi, Hubei
[2]Huangshi Aikang Hospital, Huangshi, Hubei; [3]Huangshi Central Hospital, Huangshi, Hubei (China)

Summary

Purpose: To identify structural chromosomal aberrations (SCAs) in two cases with abnormal reproductive history *Materials and Methods:* A 36-year-old male proband in a family with abnormal reproductive history were evaluated in 2015 for his wife's inability to become pregnant. Peripheral blood of proband couples, their daughter, proband's second elder sister, and third elder brother were evaluated for chromosome examination, G-banding, 30 metaphases, and five karyotypes were analyzed. Another 27-year-old female proband with abnormal reproductive history were evaluated for infertility in 2014 and 2015. The proband couples', her parents', and her elder brother's peripheral blood was drawn for chromosomal examination. *Results:* In the first case, the proband's chromosome karyotype was 46, XY, inv(1)(q25q42) and his daughter and second elder sister were 46, XX, inv(1)(q25q42). In the second case, the proband's chromosome karyotype was 46, XX, ins(8;1)(8pter→8p11.2::1p32→1p22::8p11.2→8qter;1pter→1p32::1p22→1qter). Her husband's chromosome karyotype was normal. *Conclusions:* Inv(1)(q25q42) can exist as a recessive state and can lead to male infertility and female spontaneous abortion. Ins(8;1) can lead to female spontaneous abortion. Since the two mutations may be associated with abnormal reproductive diseases, the identification of them may have an important reference value to diagnose infertility and spontaneous abortion.

Key words: Inv(1)(q25q42); Ins(8;1); Chromosomal aberrations; Infertility; Spontaneous abortion.

Introduction

Structural chromosomal aberrations (SCAs), one type of chromosome abnormality, include deletions, duplications, translocations (balanced, imbalanced, and Robertsonian), inversions and insertion.

Many infertilities and spontaneous abortions are caused by SCAs. Overall, SCAs such as t(SRY; X) and der(13;14) occur in nearly 5% in infertile men (0.5% in the general population) [1] and frequency of chromosome anomalies such as inv(1) (q13p31), t(1;10) (q41;p14), t(4;13) (p11;q11) in patients attending a fertility clinic is around 2-3% for women [2, 3]. Parental chromosomal abnormalities represent an important etiology of recurrent miscarriage. It is estimated that chromosomal abnormalities are the underlying cause in up to 50% of spontaneous abortion [4, 5]; 6% of these abnormalities are structural aberrations such as 46, XY, der(1) t(1;15) (p36.1;q22.3) mat, 46, XY, add(5) (p15.3), 46, XX, add (6) (q21), 46, XX, add (14) (p11.2), and del (X) (q28qter) [6].

Here, the authors describe two novel SCAs including inv(1)(q25q42) and ins(8;1), leading to infertility in two cases with abnormal reproductive history.

Materials and Methods

Case 1

The proband, male, 36-years-old, with normal phenotype, went to the infertility clinic of the present hospital in 2015 for his wife's inability to become pregnant in the recent three years. His wife had a 16-year-old daughter with no obvious abnormality who is their first child. Their second child was delivered with induced labor between the sixth and seventh month of pregnancy. Their third child was spontaneously aborted during circa the second month of pregnancy. Their fourth child, a male, was found with eye obliquity, salivation, walking instability, and be prone to fall at 6-years-old. His head CT examination showed pontine tumors and died three months later. His wife denied history of special drug administration during pregnancy and they were not an intermarriage.

The proband's parents both had died. The proband's third elder brother and second elder sister had no abnormal phenotypes, both had children, and had no history of abortion except his second eldest sister with one history of abortion.

Case 2

The proband, female, 27-years-old, with normal phenotype, conceived for the first time in November, 2013 but artificially aborted due to worries about adverse effects of antibiotic administration on her fetus. She conceived for the second time in August 2014, but developed arrested fetal development on around the 40th day of pregnancy. She then went to the infertility clinic of the present hospital. The couple denied family history of genetic disease and they were not intermarried.

The proband's semen was routinely detected. His wife's sex

*Co-first author

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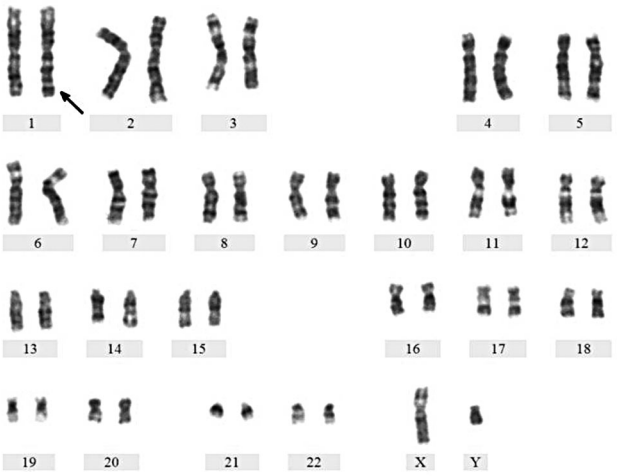

Figure 1. — The proband's chromosome karyotype: 46, XY, inv (1) (q25q42)

Figure 2. — The chromosome 1 of the proband's daughter (A) and second elder sister (B). Arrows indicate inv(1)(q25q42)

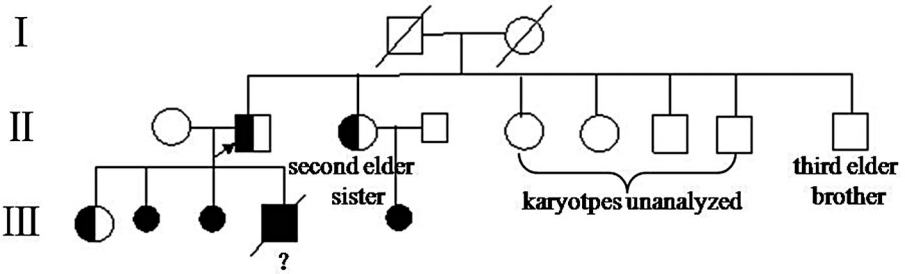

Figure 3. — The male proband's family pedigree.

Figure 4. — The proband's chromosome karyotype: 46, XX, ins(8;1)(8pter→8p11.2::1p32→1p22::8p11.2→8qter;1pter→1p32::1p22→1qter). Arrows indicate ins(8;1).

hormone, thyroid function, and vaginal secretions were detected.

Cytogenetic examination: peripheral blood of proband couples, their daughter, proband's second elder sister, and third elder brother were drawn for chromosome examination, G-banding, 30 metaphases, and five karyotypes were analyzed.

The female proband's TORCH, thyroid function, sex hormone level, seven infertility antibodies (-), leukorrhea routine, bacterial vagi nosis (BV), and thinprep cytology test (TCT) were detected. B ultrasound examination of the proband's uterus was conducted.

Cytogenetic examination: the proband couples', her parents', and her elder brother's peripheral blood was drawn for chromosome examination.

Results

Case 1

The proband's routine semen analysis was normal (homogeneous, grey-opalescent appearance, volume: 4 ml, pH: 7.5, liquification: 12 minutes, total sperm number: 49×10^6/ejaculate, sperm concentration: 20×10^6/ml, vitality: 69%, total motility (PR + NP): 58%, normal forms: 7%, WBC: 0.8×10^6/ml). His wife's sex hormone, thyroid function, and routine examination of vaginal secretions were normal.

The proband's chromosome karyotype was 46, XY, inv(1)(q25q42) (Figure 1); his daughter and second elder sister, 46, XX, inv(1)(q25q42) (Figure 2), and his third elder brother, 46, XY (Figure 3).

Case 2

TORCH for the proband was negative. Thyroid function dection showed FT3 level to be 6.29 pmo1/L. Sex hormone level and D-dimer were normal. Seven infertility antibodies (-), and leukorrhea routine, BV, and TCT were normal too. The semen routine detection of proband's husband was normal (homogeneous, grey-opalescent appearance, volume: 5 ml, pH: 7.8, liquification: 11 minutes, total sperm number: 51×10^6/ejaculate, sperm concentration: 23×10^6/ml, vitality: 73%, total motility (PR + NP): 65%, normal forms: 9%, WBC: 0.7×10^6/ml).

The proband's chromosome karyotype was 46, XX, ins(8;1)(8pter→8p11.2::1p32→1p22::8p11.2→8qter; 1pter→1p32::1p22→1qter) (Figure 4). Her husband's, her parents', and her elder brother's chromosome karyotype were normal.

Discussion

Inversion, one of the most common SCAs, also mainly balanced aberration, may lead to unbalanced gametes generated by germ cell during meiosis, which can increase the risk of absorption or can have inversion carriers. In the first case, both the proband and his second elder sister in the family, both with abnormal reproductive history, both carried inv(1)(q25q42), which could have been inherited by their parents, while inv(1)(q25q42) carried by the proband's daughter was inherited by the proband. Inv(1)(q25q42) is paracentric inversion and 245522847 nucleotide base pairs are contained in chromosome 1. The length of (q25q42) segment, 50-100 Mb theoretically, approximately accounted for one-fourth plus of that of chromosome 1. When the length of inversion segment is about 50 Mb, or 40-50% of that of chromosome 1, a small amount of asymmetric recombinant gametes may be generated. When the length of inversion segment outnumbers 100 Mb, or more than 50% of that of chromosome 1, a large number of asymmetric recombinant gametes may be generated [7]. Theoretically, the length of inversion segment in the family outnumbers 50 Mb, accounting for less than 40% of that of chromosome 1. However, chromosome 1 is the longest one in all 23 pairs of chromosomes. Therefore 40% of the length of inversion segment in that of chromosome 1 should not be regarded as a threshold determining whether asymmetric recombinant gametes may be generated. Hence a large number of asymmetric recombinant gametes may be generated by the proband. The proband and his second elder sister, both with abnormal reproductive history, both carried inv(1)(q25q42) chromosome. Therefore the inversed fragment, inv(1)(q25q42), likely caused the proband's infertility and his second elder sister's spontaneous abortion. The proband's living 16-year-old daughter, with inv(1)(q25q42) inherited from her father but without obvious phenotype, was a recessive carrier just like her second aunt. The proband's six-year-old son died of pontine tumors. Unfortunately, his karyotypes were not analyzed. Whether he was an overt patient, caused by inv(1)(q25q42) inherited from her father, is unknown. Therefore, inv(1)(q25q42) can exist in a recessive state and can lead to male infertility and female spontaneous abortion.

In the second case, the proband had normal phenotype and a history of two abortions. Her karyotype was a clockwise translocation among non-homologous chromosomes, i.e. direct insertion. Theoretically, if one of the couples is a non-homologous clockwise translocation carrier, a translocation loop can be formed in the course of meiosis. After isolation, free combination and odd swap in the translocation loop, 12 kinds of gametes can be formed. If they combine with normal gametes, 1/12 normal subjects and 1/12 carriers can be generated; the remaining are partial monomer, partial trisomy, partial monomer plus partial trisomy, and partial monomer plus double partial trisomy. Since most of the remaining category are only found in the embryos of early spontaneous abortion [8] and most of spontaneous abortion are caused by chromosomal abnormalities in the embryo or fetus [9], ins(8;1), the proband's SCAs, excluded from her husband's, her parents', and her elder brother's karyotype, might lead to chromosome abnormality of her embryos belonging to this category and might cause spontaneous abortion. Therefore, ins(8;1) can lead to female spontaneous abortion.

Inv(1)(q25q42) and ins(8;1) identified were confirmed as the first discovery by State Key Laboratory of Medical Genetics in Xiangya School of Medicine, Central South University. Since the two mutations may be associated with abnormal reproductive diseases, the identification of them may have an important reference value to diagnose infertility and spontaneous abortion.

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Corresponding Author:
HAIBO ZHU, M.D.
Clinical Laboratory, Huangshi Aikang Hospital
No. 562 Yiyang Road
Huangshi, Hubei 435000 (China)
e-mail: zhl135246@sohu.com