Asian Pacific Journal of Reproduction

Journal homepage: www.apjr.net

Document heading doi: 10.1016/S2305-0500(13)60183-9

The effects of a heterochromatin polymorphism in chromosome 6 on premature ovarian failure

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ARTICLE INFO

Article history:
Received 16 June 2014
Received in revised form 10 September 2014
Accepted 20 November 2014
Available online 20 March 2015

Keywords:
Chromosome 6
Heterochromatin polymorphism
Premature ovarian failure

ABSTRACT

Through cytogenetic analysis, heteromorphisms were detected in chromosomes 1,9,16 and Y and defined as non-phenotypic variations. The polymorphism in the centromeric heterochromatin region of chromosome 6 is a rare variant, and only five cases have been documented in the literature. In our study, we used cytogenetic and molecular techniques to detect an increase in the centromeric heterochromatin region in the short arm of both copies of homologous chromosome 6 in a premature ovarian failure (POF) case. The report of this case is important for determining the relationship between fertility and the frequency of rare variants of the centromeric heterochromatin region of chromosome 6 in the general population.

1. Introduction

Premature ovarian failure (POF) is a complex heterogeneous clinical disease that may be affected by the multiple genes that control follicle formation and is characterized by an early loss of the ovarian follicle or function[1]. The etiology of POF generates 20% of familial genetic causes and 5% of chromosome X anomalies[2]. Autosomal chromosomal abnormalities may also play a role in POF in addition to chromosome X. Any chromosomal structural rearrangements or deletions that exists in these genes may affect the formation of the POF phenotype[3].

It has been established that heterochromatin polymorphisms that were identified cytogenetically by GTL and C-band techniques are not clinically important[4]. In the general population, heterochromatin region increases, especially in chromosome 1-9,16-Y, have been identified. These heterochromatin regions consist of repeated DNA sequences and not structural genes. However, recent studies have proposed a variation in 9qh+, 9qh-, and Yqh+ that may play a role in recurrent miscarriage. Nonetheless, there are a small number of publications with clinical results and variant chromosome carriers[6,7].

The aim of this case report is to define the probable association of a heterochromatin polymorphism in chromosome 6 with POF.

2. Case presentation

A 33-year-old patient was referred to our infertility clinic for suspected female infertility. She had a history of 5 years of unprotected intercourse as well as a 15-month

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interruption of menses. She also had menopausal symptoms, such as flushing and vaginal dryness for 9 months. She had no history of pregnancy, previous surgeries or any other known medical illnesses. She reported that her parents were first cousins and that her mother had a menopausal age of approximately 45 years. Her first menstrual period began when she was 13 years old.

At the first examination, she had no physical abnormalities, and the genital evaluation was normal. Her body mass index was 21. She also had spontaneous menstruation during the evaluation. According to the transvaginal ultrasonography, the uterus was normal, the endometrium was approximately 5-6 mm, and there were two antral follicles on the right ovary and one antral follicle on the left ovary. Hormonal day 2-3 parameters were as follows: FSH:61.2 IU/mL, LH:28.1 mLU/mL, E2:31.8 pg/mL, PRL:9.56 μg/L , TSH:3.19 mIU/L, and sT4:1.13 ng/dL.

Chromosomal analysis from lymphocyte culture was performed with GTL-banding performed with a Tripsin-Leisman painting technique, and 20 metaphase chromosomes from the case were analyzed. The results of the chromosomal analysis show centromeric heterochromatin region increases located in the short arm of chromosome 6 in the whole cell (Figure 1). The centromere region increase was demonstrated with C-banding. After the cytogenetic analysis in the proband, karyotype analysis with standard cytogenetic techniques was performed on the samples from each of the case's parents, who are biologically related to each other. One of the copies of chromosome 6 had a centromeric heterochromatin region increase, which was observed in both parents [Figure 2-3]. The chromosome 6 centromere region was evaluated from interphase cells and spread metaphase platters with whole-chromosome painting FISH. It was analyzed for possible genomic imbalance with the Array GGH 8X60K method, and neither the centromere region of chromosome 6 nor any other region demonstrated an imbalance.

Figure 1. increased centromeric heterochromatin region located in the short arm of chromosome 6.3.

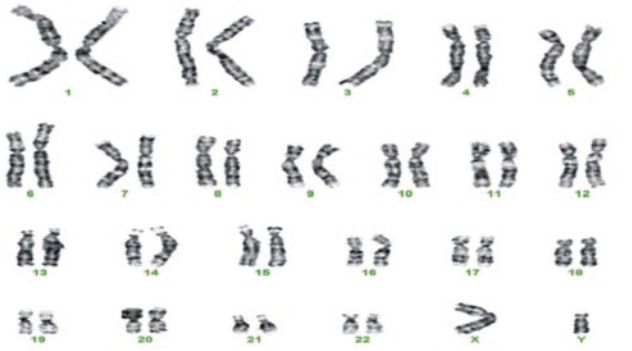

Figure 2. increased centromeric heterochromatin region located in the short arm of chromosome 6 in father.

Figure 3. increased centromeric heterochromatin region located in the short arm of chromosome 6 in mother.

4. Discussion

In this POF case, from the karyotype analysis were performed using the GTL banding method, we observed an enlargement from both homologous copies of chromosome 6 centromere regions. In our analysis, the enlargement came from both parents and the enlargement of the centromeric heterochromatin region of both copies of homologous chromosome 6. To the best of our knowledge, this is the first case in which enlargements of both copies of homologous chromosome centromeric heterochromatin regions that were associated with POF were detected.

The heterochromatin region plays a key role in chromosome structure, histone modification and gene regulation[8]. It is also known that these factors are integral in the heterochromatin region for the mechanisms of spindle fibers, chromosome movement, meiosis crossover and change of sister chromatids. During meiosis, there may be a change in the synapses areas of homologous chromosomes in the polymorphic heterochromatin region. Another mechanism, heterochromatin polymorphism, may be indicative of defective histone protein methylation.

The polymorphism of the chromosome 6 centromere region short arm was first identified by Madan and Bruinsma and was reported as a variation in 1979. These researchers also reported that the prevalence of the enlargement in the chromosome 6 C-band region is approximately 9%[9]. Jabs and Carpenter identified variant segregation as belonging to chromosome 6 and that the enlargement of the centromere region corresponded to alphoid repeat sequence amplification. They also noted that the double amplification of the repeat at the centromere of chromosome 6 might be tolerated by the genome and that there were no determined harmful effects [10]. Lin *et al*. identified the 6q11+ variant from a mother and fetus pair. This was the first variant that belongs to the q arm of chromosome 6 that has been identified. They observed FISH signals that belong to the region of the chromosome 6 variant, which was 3 fold more intense than its homologues, and there were no phenotypic effects[11]. Our case is consistent with this study. The size of the variant region shows differences between arm p and q by enlargement[12]. Goumy *et al*. identified a rare de novo 6p11 variant through prenatal diagnosis[13]. These results contrast with other research, including our own, which show that the variant is hereditary. Additionally, in the CGH Array analysis, the authors reported no genomic imbalance that was due to this variant, and our study supports this finding. Çağlayan et al. identified expansion in the centromeric regions of the p and q arms of chromosome 6 in two infertile men[14]. Their study suggests that heterochromatin variation may also be a cause of male infertility. In contrast, our case is important in demonstrating the probable association between centromeric heterochromatin variation and premature ovarian failure.

In terms of heterochromatin variation, the 9qh,16qh variations are very common. Recent studies have shown that the 9q12/qh+ variants may be important in explaining recurrent miscarriage[14, 15]. However, 6p/q variants are rare.

Our study showed that in both homologous chromosomes, centromeric heterochromatin enlargement is the first in this variation category and the third infertility case. Recent research has demonstrated that there may be an association between heterochromatin variants and recurrent miscarriage; in our case, infertility made the heterochromatin variant important. This case report underscores the relevance of determining the relationship between infertility and the frequency of rare variants in the centromeric heterochromatin of chromosome 6 in the general population.

Conflict of interest statement

We declare that we have no conflict of interest.

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