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Case Report

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A Rare Familial Paracentric Inversion in the Long Arm of Chromosome 8: Case Report and Review of the Literature

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Abstract

Background/Aim: The incidence of paracentric inversions (PAI) in the general population ranges from 0.09-0.49/1,000 and PAIs involving a relatively short chromosome segment, are generally considered to be harmless. However, PAI carriers have a very low risk to give rise to a viable zygote (3.8%).

To present a rare case of a healthy individual, carrier of an 8q paracentric inversion.

Methods: A 37-year-old man and his 30-year-old wife were referred for karyotypic analysis due to a previous miscarriage at 33 weeks of gestation. Cytogenetic analysis was performed on peripheral blood lymphocytes by GTG banding. Molecular karyotype analysis performed using Agilent G3 4x180 K CGH+SNP microarray platform.

Results: The wife had a normal karyotype 46,XX but the man's karyotype was 46,XY,inv(8)(q23.1q24.2). Karyotypic analysis of his parents revealed that his mother carried the same inversion. Molecular analysis reported no duplication or loss in or near the inverted region.

Conclusions: Review of the literature revealed the rarity of chromosome 8 paracentric inversions and showed that although the risk of a carrier to have an abnormal offspring is low, in cases of large inversions or previous abortions prenatal diagnosis should be offered by conventional and molecular cytogenetic techniques.

Keywords

Cytogenetic analysis; Molecular karyotype; Familial; Paracentric inversion; Genetic counseling

Introduction

Paracentric inversion (PAI) is a common rearrangement involving two breaks within the same chromosome arm, followed by the reinsertion of the chromosome segment into its original location after a 180° rotation. The incidence of PAI in the general population has not been clearly established, but seems to range from 0.1-0.5 % [1,2].

PAIs, especially those involving a relatively short chromosome segment, are generally considered to be harmless [3]. In heterozygous carriers, homologue pairing during meiosis is maximized by the formation of an inversion loop. When a crossover occurs, dicentric and acentric fragments can be formed and these gametes may lead to embryos that will be lost very early, usually before implantation. Thus, gametes containing unbalanced chromosomes very rarely give rise to a viable zygote (3.8%) [4].

The aim of the present report was to present a new paracentric inversion in the long arm of chromosome 8 [inv(8)(q23.1q24.2)] detected by conventional karyotyping in the male partner of a couple with a third-trimester abortion.

Case Presentation

A 37-year-old man and his 30-year-old wife were referred for karyotypic analysis due to a previous miscarriage at 32^{+6} weeks of gestation after natural conception. Post-mortem examination of the fetus showed that embryonic death was caused by acute intrauterine asphyxia due to placental maturation defect with no definite reason.

During her pregnancy, the mother suffered from gestational diabetes and obesity and was under insulin treatment. No earlier conception, pregnancy or miscarriage were mentioned and both partners reported uneventful family histories.

Methods

Cytogenetic analysis was performed on peripheral blood lymphocytes by GTG banding according to standard laboratory protocols and from each individual, 25 metaphases were examined. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature 2016 (ISCN, 2016) [5].

Molecular karyotype was performed in order to identify possible chromosomal aberrations not detectable by routine G-banded chromosomal analysis. For the analysis, the G3 4x180k CGH+SNP microarray platform with an average probe spacing of 20 kb (Agilent Technologies, Santa Clara, CA) was used. Samples were processed according to manufacturer's instructions and CytoGenomics 4.1 software was used for feature extraction and visualization of the resulting data. For annotation of genes in the deleted or duplicated genomic segments the UCSC (http://genome.ucsc.edu/) and the Database of Genomic Variants (http://projects.tcag.ca/variation/; human genome build 19) were used.

The research was ethically conducted in accordance with the World Medical Association Declaration of Helsinki. Participants were informed and gave their written consent.

Results

Karyotypic analysis showed that the wife had a normal 46,XX karyotype, while her husband was a carrier of a paracentric inversion of chromosome 8 [46,XY,inv(8)(q23.1q24.2)] (Figure 1). Karyotypic analysis of his parents revealed that his mother carried the same inversion, indicating the familial origin of this aberration. Molecular karyotype analysis reported no duplication or loss of chromosome material in or near the inverted 8q region. With the exception of microduplications and microdeletions, referring as copy number polymorphisms (CNPs), no other imbalances were

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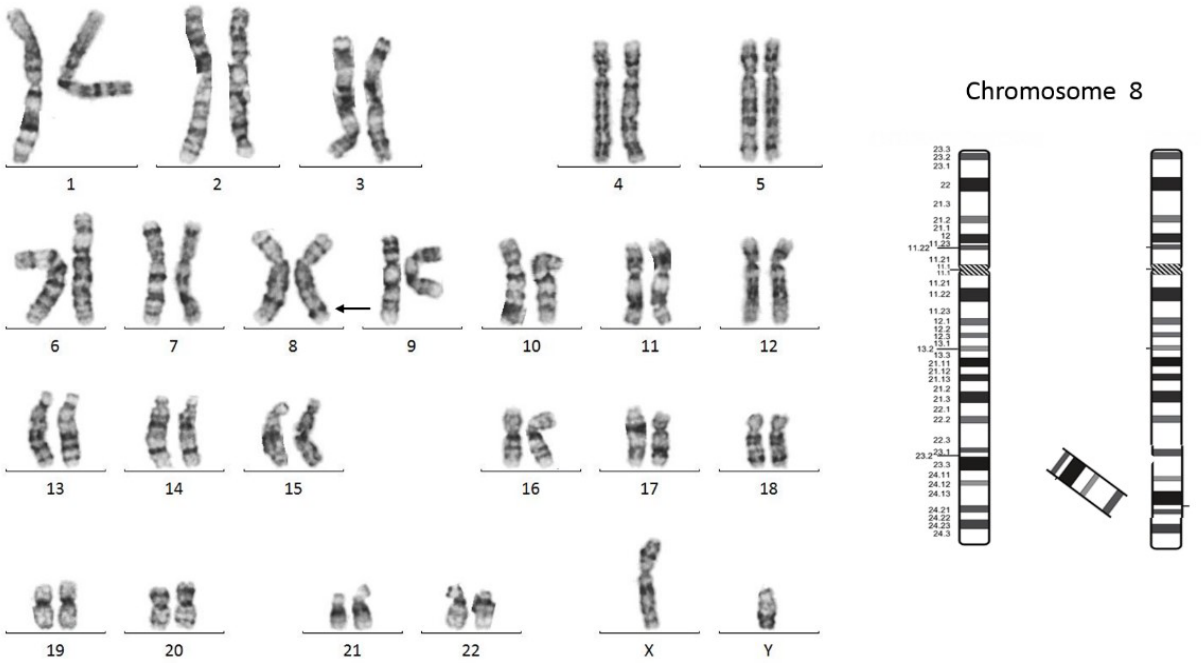

Figure 1: Karyotype 46,XY,inv(8)(q23.1q24.2).

detected.

Discussion

The present report presents a new paracentric inversion of maternal origin in the long arm of chromosome 8. To our knowledge, this case is the fourth reported 8q paracentric inversion in the literature. The carrier was a healthy man whose wife had a third-trimester abortion probably due to placental maturation defect. Based on the pathologo anatomic findings of the aborted embryo, the miscarriage seems not to be related to the paternal paracentric inversion.

The described structural abnormality is considered to be an inversion as cytogenetically it was not possible to distinguish it from an insertion due to the involvement of only one G-band in the interstitial segment.

In this case, cytogenetic analysis of the man's parents revealed that his mother carried the same paracentric inversion showing the familial origin. According to the literature, the great majority of PAIs are familial (about 90%) [6].

In general, PAI carriers have no phenotypic consequences except cases where chromosome breakpoints interrupt critical genes [3,7,8]. However, carriers of PAIs involving euchromatic regions are at an increased risk of producing unbalanced gametes and subsequently unbalanced embryos, which in most cases result in early miscarriages or stillbirths. Meiotic crossover within the inverted segment results in acentric fragments and dicentric chromosomes formation. Although the risk of a PAI carrier having a viable zygote is relatively low (3.8%), in cases where small cryptic deletions or duplications arise, the unbalanced gametes if fertilized, may result in an abnormal child with congenital abnormalities. The reproductive risk seems to be clearly related to the chromosomes involved, the size of the inverted segment (>100 Mbp) and the presence of recombination hot spots around the breakpoints within the inverted segment [6,9,10].

Furthermore, some studies have demonstrated the possible influence of inversions on the synapses and disjunction of other chromosomes (interchromosomal effect) as an alternative source of chromosomal abnormalities [10-12]. However, this phenomenon was not detected in other studies and deserves attention [6,13].

To our knowledge, in the literature only three 8q PAI cases have been reported. Specifically, Madan et al described two cases of paracentric inversion of the long arm of chromosome 8 [14]. The first was a girl with a familial inv(8)(q21-2q22) found during prenatal diagnosis performed because of a previous child with a neural tube defect. The second was a female carrier of inv(8)(q22q24) referred for infertility, oligomenorrhoea, hirsutism, and scanty pubic hair. The origin was unknown as other family members were not investigated. The third case was a man with inv(8)(q22.3q24.13) who acquired an offspring with del(8)(q23.3q24.13) and the proposed mechanism included unequal crossover in the middle of the loop leading to a deletion of a part of the inverted segment [15].

According to a large review of 446 cases with paracentric inversions of Pettenati et al. [4], PAIs have been found in all chromosomes, but their incidence was not the same. The most commonly involved chromosomes are 1, 3, 5, 6, 7, 11 and 14 and less frequently involved are chromosomes 4, 16, 17, 18, 19, 20, 21, 22, and Y. Ascertainment was primarily incidental (54.5%), mental retardation and/or congenital anomalies (22.2%), spontaneous abortions (11.4%), associations with syndromes (3.0%), and infertility (2.0%) accounted for the remainder. The most frequent PAI seems to be inv(11)(q21q23), with no increase in the rate of spontaneous abortions among carriers or their partners [16].

In conclusion, although most PAIs seem to be harmless, their clinical relevance is related to the formation of recombinant gametes that may lead to abnormal embryo. It is of great importance to define

the size of the inverted segment, the familial or *de novo* origin of PAI as well to assess if the rearrangement is a paracentric inversion or an intrachromosomal paracentric insertion since paracentric insertion have higher risk of recombination (15%) [4,17]. Genetic counseling based on the size of inverted segment should be offered in PAI carriers. In cases with large inversions and/or previous abortions, prenatal diagnosis should be offered using both conventional and molecular cytogenetic techniques. Moreover, state-of-the-art techniques including array-comparative genomic hybridization (aCGH) in pre-implantation genetic diagnosis (PGD) could have a significant effect on the reproductive outcome of the PAI carrier.

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Conflict of Interest

The authors declare no conflicts of interest.

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