

Human Cytogenetics Case Report Yet Unreported Heteromorphic Variant in Chromosome 17

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Received date: September 11, 2017; Accepted date: September 20, 2017; Published date: September 25, 2017

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Abstract

Background: Heteromorphic variants including Yq12 material, being inserted or added to autosomal chromosomes have been reported for chromosomes 1, 7, 11, 13, 14, 15, 21 and 22. Here we describe a novel insertion of Yq12 heterochromatin into a chromosome 17; to the best of our knowledge no similar cases have been reported previously.

Methods: GTG-, C-banding, fluorescence in situ hybridization (FISH), and homemade human heterochromatin specific multicolor FISH probes set (HCM-mix) were used to define the abnormality. A whole chromosome painting (wcp) probe for #17 together with a probe for Yq12 heterochromatin was hybridized to the patient sample. Additionally, Y microdeletion PCR was done to detect possible AZF subregional deletions.

Results: The male patient had normal sperm analysis and no AZF deletions on Y chromosome. GTG and C-banding showed an additional band on chromosome 17q21. FISH studies revealed that the insertion was derived from Yq12 heterochromatin.

Conclusions: The heterochromatin insertion on 17q21 originating from Yq12 chromosome did not affect the spermatogenesis of aberration carrier and is probably not the cause of infertility in these partners. However, a new heteromorphic variant was identified in this case.

Keywords: Heteromorphic variants; Chromosome 17; Yq12 chromosome; Infertility; Insertion

Introduction

Chromosomal heteromorphisms are still a major challenge in routine cytogenetic diagnostics, as a mix up of a benign variant with a meaningful chromosomal imbalance has to be avoided. Even though euchromatic and heterochromatic heteromorphisms are known since decades, they were just recently systematically cataloged [1,2] and made available in an open access database [3]. About 200 euchromatic and heterochromatic variants, each, are reported in the literature by now [3]. Heteromorphic variants including Yq12 material, being inserted or added to autosomal chromosomes have been reported by now for chromosomes 1, 7, 11, 13, 14, 15, 21 and 22 [3].

The Y-chromosome is essential for sex determination, early sexual differentiation and control of spermatogenesis in mammals [4,5]. The incidence of Y-autosome translocations is ~1: 2,000 in general population [6,7] and may involve any segment of the Y chromosome [8,9]. Male infertility occurs when the breakpoint lies in the region of the azoospermia factor (AZF) locus at Yq11 [10]. However, some cases provided evidence that breakpoints in the Yq12 heterochromatic

region may also be associated with male infertility [11,12] and some breakpoints in the Yq11 euchromatic region may also be present in fertile males [13]. Apart from some exceptions associated with fertile or subfertile phenotypes [11,14] Y-autosome translocations usually lead to male infertility. The most common Y-autosome translocations are those occurring between an acrocentric short arm and Yqh and are usually identified as either of the derivative chromosomes; a satellited Yq (e.g., der(Y)t(Y;15)(q12;p11.2)) or a D/Gph+ chromosome (e.g., der(15)t(Y;15)(q12; p11.2)). Other Y-autosome translocations have been reported in at least 35 male patients. Most of these Y-autosome translocations, with both Yq11.2 and Yq12 breakpoints, occurred as de novo events and were associated with azoospermia or infertility [9,15,17].

A segment of Y chromosome heterochromatin can also be inserted into another chromosome and it may be without any phenotypic effect. Ashton-Prolla et al. [18] reported this special rearrangement during a prenatal diagnosis, with the karyotype only interpretable after the father had been studied. He had a segment from Yq12 inserted into chromosome 11 at band 11q24: 46,XY,der(11)ins(11;Y)(q24;q12q12). He had inherited the ins(11;Y) from his mother, and her clinically healthy status, and subsequently his infant daughter's clinically healthy status, attested to the innocuousness of this variant chromosome.

Another similar case is described in Spak et al. [19], of a harmless C-band positive insertion at 11q23.2; the origin of the heterochromatin could have been an autosome or the Y chromosome. Also, insertions of Yq12 material in to 1q12 [20], and in 15q10 [21,22] were reported before. These Y heterochromatin translocations/insertions are to be regarded as variants without phenotypic consequence [6].

Here we describe a novel kind of insertion of Yq12 heterochromatin into a chromosome 17, as confirmed by FISH analysis. No similar cases were reported in previously published studies.

Patient

A 42 years old Bosnian male patient and his 35 years old female partner were referred to Human Genetics Laboratory, Clinical Center of the University of Sarajevo for karyotyping. The couple has been trying to conceive for five years. During this period, the female patient had two extrauterine pregnancies, which resulted in the removal of both fallopian tubes. Subsequently, IVF procedure was initiated twice, both resulting in no implantation. Semen analysis of male patient was normal. No miscarriages and problems with fertility were noted in their family histories.

Materials and Methods

GTG- and C-banding according to standard procedures were applied for karyotype analyses. Molecular cytogenetics using fluorescence in situ hybridization (FISH) using the following probes and probe sets was subsequently done: LSI RARA (in 17q21; Abbott Molecular) LSI TP53 (in 17p13.1; Abbott Molecular). Also, the homemade human heterochromatin specific multicolor-FISH probes set (HCM-mix) [23] and a whole chromosome painting (wcp) probe for #17 together with a probe for Yq12 were hybridized. As counterstain 4',6-diamidino-2-phenylindole DAPI was used.

Additionally, Y microdeletion PCR (GML Y Chromosome Microdeletion Detection System Kit, Altendorf, Switzerland) was applied acc. to manufacturer's instructions.

Results

Using GTG-banding, an additional band was identified to be present in the long arm of one chromosome 17 in male patient's karyotype (Figure 1a). The band looked like an insertion of extra heterochromatin into 17q21. C-banding confirmed this suggestion (Figure 1b). FISH analysis using probes specific for RARA (17q21) and TP53 (17p13.1) substantiated that there is a strongly stained DAPI-positive band inserted in 17q21 (Figure 2). The HCM-FISH-probeset revealed that the inserted material was derived from Yq12; also in Figure 2 the confirmatory FISH experiment using a wcp probe for chromosome 17 together with a probe for Yq12 is depicted.

Additionally, Y microdeletion PCR analyses excluded a common deletion (like azoospermia factor=AZF genes) in normal Y-chromosome, which could be causative for the infertility of the studied patient (result not shown) (Figure 3).

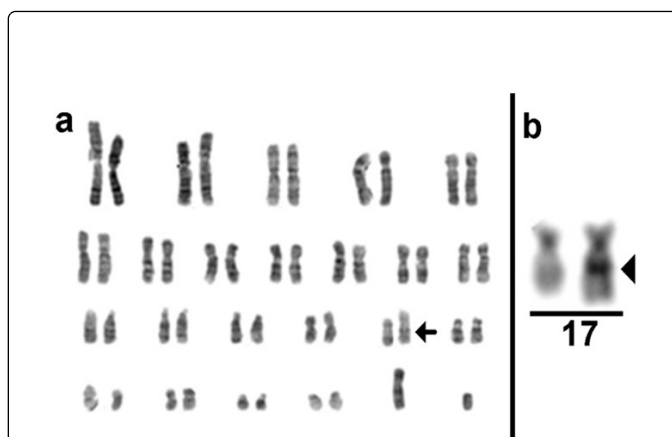


Figure 1: Patient's karyotype performed by: a) GTG-banding; one chromosome 17 was enlarged with an extra G-positive band (arrow). b) Partial karyotype after C-banding; one chromosome 17 shows extra C-positive region (arrowhead).

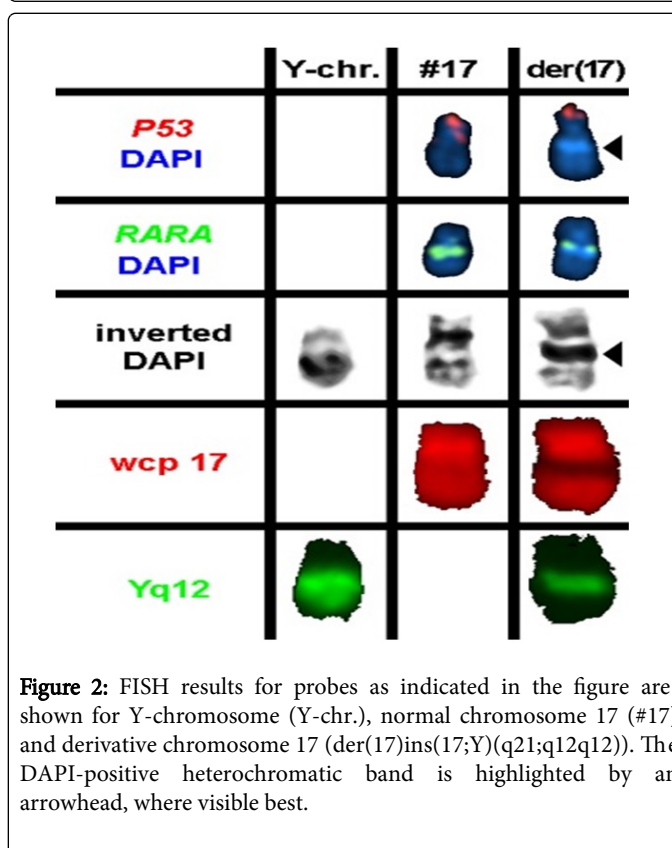


Figure 2: FISH results for probes as indicated in the figure are shown for Y-chromosome (Y-chr.), normal chromosome 17 (#17) and derivative chromosome 17 (der(17)ins(17;Y)(q21;q12q12)). The DAPI-positive heterochromatic band is highlighted by an arrowhead, where visible best.

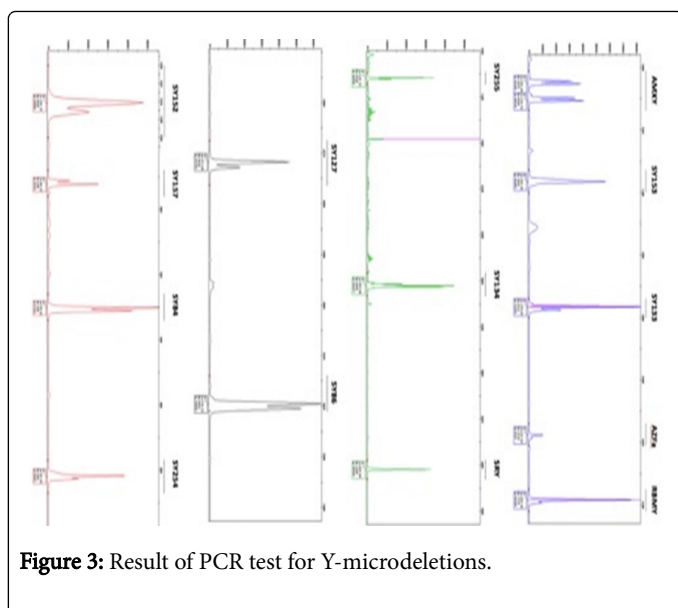


Figure 3: Result of PCR test for Y-microdeletions.

Discussion

Here we report a new heterochromatic heteromorphism present in an apart from infertility phenotypically normal male. As well-known from literature it is not unusual to detect chromosomal heteromorphisms in this group of patients (1; 24). As no parental studies were possible in this case it could not be clarified if the rearrangement was de novo or familial variant.

Due to the absence of AZF deletions and normal sperm analysis of male patient, it can be concluded that the above-described aberration - the insertion of heterochromatin on 17q21 originating from Yq12 chromosome - did not affect the spermatogenesis of aberration carrier and this is probably not the cause infertility in these partners.

Overall, the present case confirms that human heteromorphic patterns are underdiagnosed, underreported and that there is still a lot of variation out there waiting to be detected, even on the cytogenetic level of the human genome.

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