

CASE REPORT

MOLECULAR CYTOGENETIC CHARACTERIZATION OF AN *inv*(Y)(p11.2q11.221~q11.222) IN A SYRIAN FAMILYAl-Achkar W^{1,*}, Wafa A¹, Al-Ablog A¹, Moassass F¹, Liehr T²

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ABSTRACT

Constitutional chromosomal abnormalities are an important cause of miscarriage, infertility, congenital anomalies and mental retardation in humans. Pericentric inversions of the human Y-chromosome [*inv*(Y)] are rather common and show an estimated incidence of 0.6-1:1,000 in males in the general population. Most of the reported cases with *inv*(Y) are familial. For carriers of pericentric inversions the risk of mental retardation or multiple abortions is not apparently increased and there is no relation with abnormal phenotypic features. Polymerase chain reaction (PCR) analysis to detect microdeletions along the Y-chromosome as well as cytogenetic and fluorescence *in situ* hybridization (FISH) analysis were done to delineate the characteristics of an *inv*(Y) in a Syrian family. Thus, we present a detailed molecular-cytogenetic characterization of a father and his two sons having an *inv*(Y)(p11.2q11.221~q11.222) with varying mental retardation features but otherwise normal phenotype.

Keywords: Y-Chromosome; Inversion; Mental retardation; Fluorescence *in situ* hybridization (FISH); Ampli-conic fertility genes.

INTRODUCTION

Pericentric inversions of the human Y-chromosome [*inv*(Y)] are rather common and show an estimated incidence of 0.6-1:1,000 in males in the general population [1]. Most of the reported cases with *inv*(Y) are familial [2] and may include progeny with aneuploidies, preferentially +21,XXY and other chromosomal syndromes. For the carriers of *inv*(Y) the risk of mental retardation, multiple abortions or phenotypic abnormalities is not apparently increased [3,4].

It makes sense that *inv*(Y) neither impedes the production of normal sperm nor does it predispose non disjunction of other chromosomes in the progeny [5-6], *i.e.*, it is normally considered as a chromosomal heteromorphism [3-4]. However, *inv*(Y) has also been reported in association with infertility [7] and in patients with either concomitant minute Yq11 deletions [8] or a breakpoint in the 'deleted in azoospermia' (*DAZ*) gene cluster region [9]. In this report, we present a detailed molecular and molecular cytogenetic characterization of a family having an *inv*(Y) (p11.2q11.221~q11.222) over two generations and different clinical outcomes.

MATERIALS AND METHODS

Patient History. A 37-year-old male, his unrelated 32-year-old wife and the two sons of the family are reported, aged 15 and 17, respectively. The mother was healthy and had a karyotype 46,XX. Father and

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both sons had varying features of mental retardation but otherwise normal phenotypes. The parents did not have any history of miscarriages.

Cytogenetic and Molecular Cytogenetic Analyses. Cytogenetic analysis using GTG-banding was performed according to standard procedures [10]. A minimum of 20 metaphases analyzed from stimulated peripheral blood cultures were analyzed. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature [11].

Fluorescence *in situ* hybridization (FISH) was carried out on the metaphases using commercially available probes (LSI SRY), subtelomeric for Xp/Yp and Xq/Yq and centromeric for Y (DYZ3) (Abbott Molecular/Vysis, Des Plaines, IL, USA). Additionally centromere-near probes of the previously reported subcentromeric multicolor-FISH (subcenM-FISH) mix were applied [8]. A minimum of 20 metaphases spreads were analyzed. The results were evaluated on a fluorescence microscope (AxioImager.Z1 mot; Zeiss, Jena, Germany) equipped with appropriate filter sets to discriminate between a maximum of five fluorochromes and the counterstain DAPI (4',6-diamino-2-phenylindole). Image capturing and processing were carried out using an Isis imaging system (MetaSystems, Altusheim, Germany).

Molecular Analysis. The azoospermia factor (AZF) microdeletions on the Y-chromosome were detected according to the procedure of Al-Achkar *et al.* [12].

RESULTS

Cytogenetic, Molecular Cytogenetic and Molecular Analyses. The karyotype determined by GTG-banding was 46,X,der(Y) (Figure 1). Fluorescent *in situ* hybridization using commercial Y-chromosome-specific probes revealed that sex determining region (SRY), AZF, Yq-heterochromatin and subtelomeric probes were in the expected positions (data not shown). Only the subcenM-FISH mix results showed the presence of a pericentric inversion (Figure 2) characterized as 46,X,inv(Y)(p11.2q11.221~q11.222) (20/metaphases). On the molecular level, the breaks appeared between the centromere and RP11-115H13, *i.e.*, positions 6,919,727 and 11,300,000 as well as slightly distal from RP11-71M14, *i.e.*, from position 15,173,599. Thus, the main cluster of RNA-binding motif Y-chromosome (RBM Y) in Yq11.223

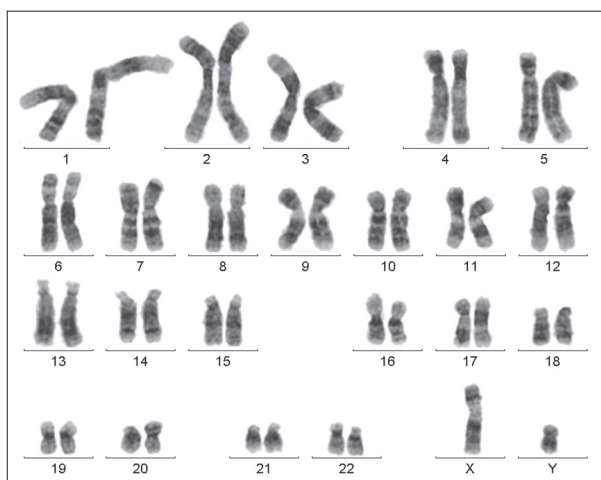


Figure 1. Karyotype from a peripheral blood meta-phase of the one of the three patients showing 46,X, der(Y).

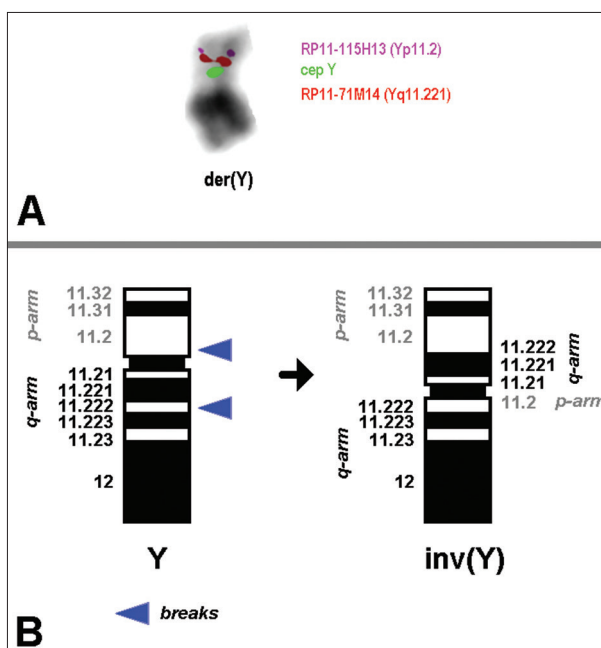


Figure 2. Centromeric probe for the Y-chromosome and centromere-near probes derived from Yq and Yp revealed the breakpoints of the pericentric inversion as Yp11.2 and Yq11.221~q11.222; the FISH results are depicted in A. B Schematic drawings of a normal and the derivative Y-chromosome are shown.

to Yq11.222 and the proximal deleted azoospermia) *CDY* (gene in Yq11.221. Molecular genetic analysis for 26 sequence-tagged sites) STSs (Y-chromosome specific excluded AZF microdeletions in the family (data not shown).

DISCUSSION

Constitutional chromosomal abnormalities are an important cause of miscarriage, infertility, congenital anomalies, and mental retardation in humans. The frequency of structural chromosomal abnormalities has been estimated as 0.25% in live-born infants [13]. Chromosomal polymorphisms of the constitutive heterochromatin regions of chromosomes 1, 9, 16, and the Y-chromosome have been reported [14].

Mental retardation results from a defect in the structure and function of the neuronal synapse. Its worldwide incidence [intelligence quotient (IQ <70)] is ~2.0-3.0%. Males are found to be more affected than females. The risk of mental retardation is higher in children with congenital structural defects [15]. The cause of mental retardation may be genetic (30.0%) or environmental, congenital or acquired. Chromosomal aberrations account for 15.0% of mentally retarded individuals. Several types of structural aberrations are also known to cause mental retardation, the common ones being deletions, duplications, inversions, translocations and/or isochromosome formation [15].

Isodicentric Y chromosomes [idic(Y)] are formed by homologous crossovers between opposing arms of palindromes on sister chromatids. The authors propose that intrapalindrome sequence identity is maintained *via* non crossover pathways of homologous recombination. DNA double-strand breaks that initiate these pathways can be alternatively resolved by crossovers between sister chromatids to form idic(Y) chromosomes, with clinical consequences ranging from spermatogenic failure to sex reversal and Turner syndrome [6].

In all inv(Y) chromosomes cases previously described, which appear metacentric after banding analysis, the inversion breakpoints on the short arm in Yp11.2 fall in a gene-poor region of X-transposed sequences proximal to the pseudo autosomal regions (*PARI*) on the X- and Y-chromosomes at the end of the short (p) arm SRY [16,17]. However, in our familial cases, the long arm inversion breakpoint maps proximal to the fertility genes *CDY* and *DAZ* in Yq11.223, resulting in our familial inv(Y)-type II. A similar familial inv(Y) case has been published [17].

In conclusion, we present a detailed molecular-cyto-genetic characterization of a family who had an inv(Y)p11.2q11.221~q11.222 with mental retardation features but an otherwise normal phenotype.

However, molecular analysis of some genes implicated in mental retardation and detection of small gains or losses of genetic material using appropriate new high-resolution test methods and/or genome sequencing should be considered for future studies.

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Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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