# Case Report

# Tetrasomy 15q11-q13 Diagnosed by FISH in a Patient with Autistic Disorder

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We report the case of a Moroccan boy with mental retardation, hyperactivity, epilepsy, developmental problems and behavioural disorders. Cytogenetic analysis showed the presence of a supernumerary marker chromosome. Molecular cytogenetics allowed us to determine the marker as an inverted duplication of chromosome 15. It is the first case of a Moroccan patient with tetrasomy 15q in which fluorescence in situ hybridization (FISH) enabled us to specify the diagnosis. Interestingly, this patient has an infantile autism with cytogenetic abnormalities on chromosomal region 15q11-q13 as reported in patients with Autistic Disorder.

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# 1. INTRODUCTION

For more than 12 years, scientists have noticed that some individuals with autism also have a chromosomal change involving specific part of chromosome 15 [1]. Trisomy or tetrasomy of the 15q11-q13 region has also been reported in some autistic patients with varying degrees of mental retardation [2–4]. This report describes a male patient with autistic disorder, and a supernumerary marker chromosome (SMC). Molecular cytogenetic investigation using FISH method allowed us to characterize the marker as an inv dup(15) including the Prader Willi/Angelman locus. Therefore, this patient has a tetrasomy for the 15q11-q13 chromosomal region. This observation reinforces the hypothesis that additional copies of proximal chromosome 15 segment may be causally related to autism.

# 2. CASE REPORT

The patient, an 8-year-old male, is the sixth child born to nonconsanguineous healthy parents. The mother and father were, respectively, 45 and 65 years old. The patient has developmental delay, mental retardation, hyperactivity, epilepsy, antisocial behavior, abnormal language skills and inability to maintain social approaches. He presents also stereotypies, including hand flapping, hand-clapping over plane surfaces without growth delay or microcephaly. At that time, the diagnosis of autistic disorder (DSMIV) was established. Physical examination revealed hyperlaxity of joints, hypotonia, and no evident facial dysmorphism (see Figure 1); and the electroencephalogram showed frequent bilateral diffuse fast rhythms during sleep. Computerized tomography scanning of brain was normal.

#### 3. MATERIALS AND METHODS

Conventional cytogenetic analyses were performed in the Department of Medical Genetics at the National Institute of Health in Morocco. Cell culture, cytogenetic preparation GTG and RHG banding were performed according to standard protocols. Briefly, this included 72 hours culture of cells in RPMI 1640 medium supplemented with 10% fetal bovine serum. Harvesting was accomplished using Colcemid incubation. The metaphase preparations were fixed with methanol and acetic acid. The SMC was further characterized by fluorescence in situ hybridization (FISH) with a whole chromosome 15 painting probe, WCP15 (Vysis, Downers Grove, Ill, USA) and the Prader Willi/Angelman probe which contains three locus/region-specific probes: D15Z1 at the centromeric region (spectrum green), D15S10 at the 15q11-12 PWS/AS critical region (spectrum orange), and PML at 15q22 (spectrum orange) (Vysis, Downers Grove, Ill, USA). Hybridizations were performed following



FIGURE 1: The phenotype of the patient.

manufacturer's instructions and 30 cells were counted for each probe.

#### 4. RESULTS

RHG and GTG banding analysis of the patient's chromosomes revealed an SMC (see Figure 2). Thus the karyotype is 47, XY,+mar [21 cells] according to the ISCN (1995). FISH study with chromosome 15 painting probe showed a complete hybridization of the marker in 30 cells scored. To further characterize this marker, FISH analysis was carried out using the Vysis Prader Willi/Angelman region probes. The D15Z1 probe showed two signals for the centromeric region as the D15S10 probe and no signal for the PML probe suggesting an inv dup(15) including the PWS/AS region (see Figure 3). The karyotypes of both parents were normal. Therefore patient's karyotype was interpreted as 47,XY,+mar.ish idic(15)(wcp15+, D15Z1++, D15S10++, PML-) de novo.

#### 5. DISCUSSION

Cases with partial trisomy of a specific portion of chromosome 15 (15q11-q13) have been reported in a considerable number of individuals with autism or with pronounced autistic behavior [1, 5].

Supernumerary marker chromosomes occur at a frequency of 0.3 per 1000 live births and around 60% of all SMCs are designated "SMC(15)s." SMC(15)s were first described by Van Dyke et al.[6] and were consist in two inverted copies of the short arm, centromere(s) and proximal long arm of chromosome 15. The majority of SMC(15)s are dicentric, with one inactivated centromere, and are also called "pseudodicentric chromosome 15" or "inv dup(15)." Using conventional cytogenetic analysis, two groups of SMC(15)s are distinguished: the first one is small SMC(15)s which are metacentric chromosomes without euchromatic materiel, the second is large SMC(15)s which are acrocentric chromosomes containing two copies of the 15q11-q13 region. Small SMC(15)s can be familial or de novo and are not directly associated with an abnormal phenotype. In all cases, the SMC(15)s were maternally derived [7].

In this article we report a male child with tetrasomy of the 15q11-q13 chromosomal region and autistic disorder associated with mental retardation, developmental problems and behavioral disorders, epilepsy and no evident dysmorphy. Compiling classical and molecular cytogenetics, the kary-otype was demonstrated as 47,XY,+mar.ish idic(15)(wcp15+, D15Z1++, D15S10++, PML-) de novo. The parental origin of this SMC could not be determinated.

Cytogenetic abnormalities found at the 15q11-q13 region are reported most frequently in patients with autism, up to 1% to 4%. The chromosome region 15q11-q13 is known for its instability and many rearrangements may occur in this imprinted segment: deletion associated either with Angelman Syndrome (AS) or with Prader-Willi Syndrome (PWS) according to parental origin translocations, inversions, and supernumerary marker chromosomes formed by inverted duplication of proximal chromosome 15. Interstitial duplication and triplication are much less frequent [8]. Inherited duplications are of maternal origin and seem to cause autism by creating an over abundance of product from the nonimprinted maternally derived genes [8]. The inv dup(15) or idic(15) syndrome displays distinctive clinical findings represented by hypotonia, developmental delay/mental retardation, difficult to control epilepsy, and autistic behavior [5].

Several genes are incriminated in the unrests of the autistic disorder bound at the region 15q11-q13. Tetrasomy of these genes, as seen in inv dup(15) syndrome, may alter the GABA receptor activity, upon which the major CNS inhibitory mechanisms rely. This alteration could represent the biological basis for some clinical manifestations of the inv dup(15), such as seizures, hyperactivity, aggressiveness, and autistic disorder. Of interest, linkage disequilibrium between a marker in the g-aminobutiric acidA receptor subunit gene, GABRB3 155CA-2, and autistic disorder has been reported by Battaglia [5]. UBE3A is another candidate gene for autistic disorder, because of its position in this region and its known association with Angelman syndrome, a genetic disorder which share some symptoms in common with autistic disorder [9]. Epigenetic studies in this region recently identified ATP10C as another imprinted gene that may contribute to autistic disorder [10].

A suggested mechanism of formation of inv dup(15) involves illegitimate recombination between homologous chromosomes followed by nondisjunction and centromere inactivation. Proximal chromosome 15q is believed to be highly unstable as evidenced by its frequent involvement in structural rearrangements. The heterogeneous nature of the breakpoints involved in these chromosomal abnormalities suggests that either several low-copy repeat sequences are involved in the genesis of these chromosomal abnormalities or the same repeat sequence is located in many places throughout proximal 15 [11].

In conclusion, this observation approves the implication of the region 15q11-q13 in the autistic disorder/behavior,



FIGURE 2: (a) A partial R-banding karyotype; (b) a partial GTG-banding karyotype.



(a)

(b)

FIGURE 3: Metaphases hybridized (a) with WCP15; (b) with D15S10/PLM. Two normal copies of chromosome 15 displayed the expected centromeric signals and signals mapped at q11-q13 and q22. The der(15) has two copies of the centromeric signal and a duplicated signal for D15S10, suggesting tetrasomy 15q11-q13.

and these chromosomes 15 appear to hold particular promise in the search for candidate genes.

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