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Case Report

De Novo Balanced Translocation t (7;16) (p22.1; p11.2) Associated with Autistic Disorder

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The high incidence of de novo chromosomal aberrations in a population of persons with autism suggests a causal relationship between certain chromosomal aberrations and the occurrence of isolated idiopathic autism. We report on the clinical and cytogenetic findings in a male patient with autism, no physical abnormalities and a de novo balanced (7;16)(p22.1;p16.2) translocation. G-banded chromosomes and fluorescent in situ hybridization (FISH) were used to examine the patient's karyotype as well as his parents'. FISH with specific RP11-BAC clones mapping near 7p22.1 and 16p11.2 was used to refine the location of the breakpoints. This is, in the best of our knowledge, the first report of an individual with autism and this specific chromosomal aberration.

1. INTRODUCTION

Autism is a relatively common and heterogeneous neuropsychiatric disorder characterised by reduced social and interindividual contacts and interactions. Autism usually starts in early childhood. Complete absence of eye contact and speech can be observed in severe forms of autism [1]. Its incidence is estimated at about 1/1000 to 1/2000 with a biased male-to-female ratio of three or four to one (3-4 : 1) [2]. Studies of familial cases have demonstrated that genetic factors are involved in the aetiology of autism [3]. A number of balanced and unbalanced chromosomal aberrations have been found to be associated with autism [4–6].

In this study, we describe a reciprocal translocation t(7;16)(p22.1;p11.2) that occurred de novo in a 10-year-old boy with autism and psychomotor retardation and only minor additional anomalies or dysmorphic features. Neither chromosomal breakpoint has been mentioned in previous reports of cytogenetic aberrations seen in patients with autistic behaviour.

2. CASE REPORT

The 10-year-old patient is the younger of two children born at term from nonconsanguineous healthy parents. The father and the mother were, respectively, 34 and 30 years old when the child was born. Pregnancy was uneventful. Delivery was by caesarean section secondary to a narrow basin. Birth weight was 3350 kg, and no recognized malformations were noted. His older sister is healthy and developmentally normal.

Patient's psychomotor delays were noticed in the first months of life by his parents; they also reported frequent crying and sleep disturbances. He was unable to maintain eye contact and presented many motor stereotypes and ritualistic behaviours such as cutting papers into small pieces and aligning objects. Clinical assessment showed a boy with no dysmorphic signs (see Figure 1).

At the age of 4 years and 11 months, the patient was examined by an experienced child psychiatrist who found impairments in social interaction and communication according

to the Diagnostic and Statistical Manual-revision 4 (DSM-IV) and the Autism Diagnostic Interview (ADI-R), French version 1993, criteria and made the clinical diagnosis of autism.

Routine hearing tests and amino acid chromatography were normal. Brain CT scan revealed a cerebellar mega-cysterna in the posterior fossa and a temporal arachnoidal cyst. The electroencephalogram was normal. Southern blot analysis revealed the absence of FRAXA mutation.

3. MATERIALS AND METHODS

Chromosomal abnormalities have been identified by using traditional cytogenetics and fluorescent in situ hybridization (FISH).

Chromosomes were prepared from phytohemagglutinin (PHA) stimulated peripheral blood lymphocytes of the proband and his parents following standard procedures. The healthy sister was not available for analysis. All chromosome preparations were G-banded and then analysed.

For FISH analysis, metaphase spreads obtained from an Epstein Barr virus (EBV) immortalised cell line from the patient were hybridised with bacterial artificial chromosome clones (BACs). The RPCI-11 BAC clones covering genomic regions on both chromosomes were selected according to the UCSC Genome browser (http://www.genome.ucsc.edu/) and Ensembl genome database (http://www.ensembl.org/Homo_sapiens/). They were provided by BACPAC resource centre (BPRC) (http://bacpac.chori.org) and professor Mariano Rocchi (University of Bari, Italy). Thesequence limits of the BACs were defined according to DECIPHER database (https://enigma.sanger.ac.uk/perl/PostGenomics/decipher).

BAC clones were biotinylated with biotin-11-dUTP (Sigma) by nick translation using the Bio Nick labelling system (Invitrogen Life Technologies). For the double colour FISH experiment, one probe was labelled with biotin-11-dUTP and the second probe, a commercially one, with Rhodamine (QBiogen).

4. RESULTS

Routine and high-resolution chromosome studies revealed a de novo translocation carried by the proband. The G-band pattern suggested a balanced translocation involving 7p22 and 16p11.2 and established the karyotype as 46,XY,t(7;16)(p22; p11) (see Figure 2). The parent karyotypes were normal. To identify the translocation breakpoints, we used 16 bacterial artificial chromosome clones (BACS) from 7p22 and 16p11 in fluorescence in situ hybridization (FISH) analysis (see Table 1).

As shown in Figure 3(a), the RP11-730B22 BAC hybridized to both derivative 7 and the derivative 16 and the normal chromosome 7, but not to the normal chromosome 16, indicating that this clone spans the translocation breakpoint on chromosome 7.

Although we did not identify the actual sequence of the breakpoint on 7p22.1, we located it by BAC-FISH mapping between nucleotides 4933257 and 5107654.

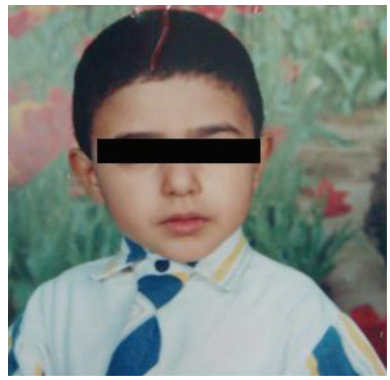


Figure 1: The phenotype of the patient.

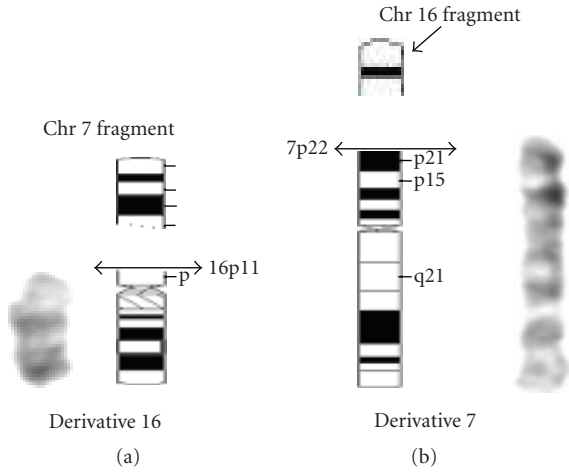


Figure 2: Partial GTG-banding karyotype of the patient. The patient derivative chromosomes 7 and 16 are shown. By comparing both respective ideogrammed chromosomes, the breakpoints were located in 7p22 and 16p11.2.

According to Ensembl genome database (May 2006 version), there are 3 coding sequences corresponding to NP_976327.1, RBAK (RB-associated KRAB zinc finger) and RNF216L or Q6NUR6 (E3 UBIQUITIN LIGASE TRIAD3 EC6.3.2.) genes.

Seven but four BAC clones located on 16p11.2 gave two distinct hybridization signals on the normal 16p and the derivative 16 (see Table 1). The overlapping BAC, RP11-264M14, hybridized to both derivative 16 and derivative 7 chromosomes and to the normal chromosome 16, but not to the normal chromosome 7 (see Figure 3(b)). The clone RP11-264M14, on 16p11.2, was found to be devoid of known genes.

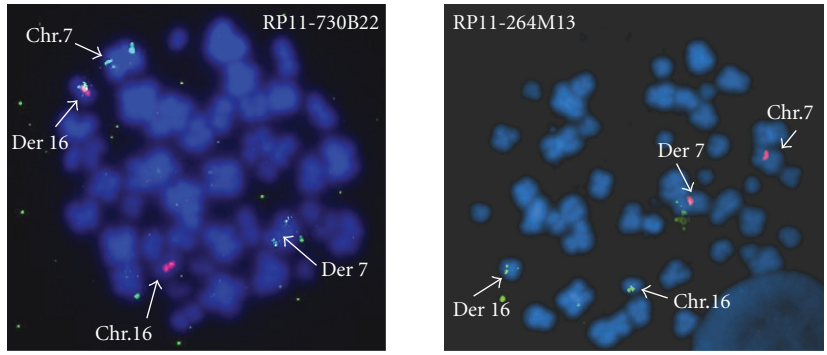
5. DISCUSSION

Genetic studies have yielded suggestive linkage and association to several different chromosomal regions, but up to now, the large number of association studies using a candidate gene approach has had limited success [7–10]. As an

Table 1: FISH results using BAC clones on 7p and 16p regions.

RP11 clone ID	Map position	Start*	End*	FISH signal on normal chromosome 7	FISH signal on Derivative 7	FISH signal on normal chromosome 16	FISH signal on Derivative 16
368N21	16p11.2	29408699	29609853	−	+	+	−
261H5	16p11.2	31120739	31307726	−	+	+	−
120K18	16p11.2	31163677	31329206	−	+	+	−
264M14	16p11.2	33282423	33452774	−	+	+	+
341P6	16p11.2	34263016	34452072	−	+	+	+
104C4	16p11.2	33362222	33555929	−	−	+	+
488I20	16p11.2	34359841	34490213	−	−	+	+
449P15	7p22.3	885103	1079306	+	−	−	+
42B7	7p22.2	4126462	4281105	+	−	−	+
33P21	7p22.1	4559141	4711177	+	−	−	+
32P3	7p22.1	4711178	4751000	+	−	−	+
160E17	7p22.1	4751001	4911018	+	−	−	+
805D5	7p22.1	4911019	4933256	+	−	−	+
730B22	7p22.1	4933257	5107654	+	+	−	+
147A22	7p22.1	5183822	5357984	+	+	−	−
1275H24	7p22.1	5427168	5510299	+	+	−	−
425P5	7p22.1	6233987	6446613	+	+	−	−

+: presence of the signal hybridization.
−: absence of the signal hybridization.
*: nucleotide position according to DECIPHER (https://enigma.sanger.ac.uk/perl/PostGenomics/decipher).



(a) (b)

Figure 3: FISH analysis of the translocation breakpoints: (a) FISH analysis with the BAC RP11-730B22 (green) located in 7p22.1 and a centromeric probe of chromosome 16 (red), shows that this BAC is spanning the breakpoint on chromosome 7. (b) FISH analysis with BACs RP11-264M14 (green) showed that it spans the translocation breakpoint located on 16p11.2. It was hybridised with a chromosome 7 centromeric probe (red). (Chr.: chromosome, Der.: derivative).

alternative approach, the characterisation of different types of chromosomal abnormalities could result in the identification of candidate genes for autism [11, 12]. Chromosomal abnormalities detected by cytogenetics or molecular cytogenetics are of major aid to locate relevant genes. About 3–5% of autistic patients have a chromosome abnormality visible with cytogenetic methods [13]. Almost all chromosomes have been involved including translocations and inversions resulting in disruption of genes at the breakpoints [14, 15].

Balanced chromosome rearrangements are observed at a significantly increased rate. Gillberg and Wahlström [16], in an epidemiological study done on 66 individuals with autism located in Sweden, found that less than 5% of the group had major chromosomal abnormalities. The same rate was found by Castermans et al. [17] when they karyotyped 525 individuals with idiopathic autism. This rate is much higher than would be expected from a general population (1/2000 for a reciprocal translocation and 1/10000 for an inversion)

Table 2: Autism related breakpoints on 7p22p and 16p11.2.

Chromosome	Karyotype	Phenotype	Reference
Chr16	46, XX, dir dup(16)(p11.2p12.1)	autism, mild mental retardation	Finelli et al. [20] Engelen et al. [21]
Chr16	46, XY, dir dup(16)(p11.2p12) de novo	autistic behaviour, psychomotor retardation	Carrasco Juan et al. [22]
Chr16	46, XY, inv(2)(p11.2q13), 16qh-	autism	Vorsanova et al. [23]
Chr7	del (7)(p22.2p22.2)	autism	Yu et al. [24]

[18]. This suggests that certain chromosome aberrations like translocations, deletions, or inversions may involve genes acting as susceptible factors for autism.

In this article, we describe a 10-year-old child carrying a de novo balanced (7;16)(p22.1;p16.2) translocation associated with an autistic disorder, psychomotor delays, and no dysmorphic features.

This case represents both an unusual and useful opportunity to examine and compare the cytogenetic and the common physical features with the previously reported cases of autism and these specific regions. In Table 2, an overview is given of all patients with chromosomal anomalies involving the 7p22.1 and 16p11.2 regions that have been described in the literature. In the best of our knowledge, it is the first time the autism phenotype has been associated with a translocation in these specific chromosomal regions.

Chromosome 16p has been identified by a number of genome screens for autism and is likely to contain an autism-susceptibility variant. The 7p locus has been less consistently reported than the chromosome 16p one. Both regions remain an important area for future research [19].

Regarding the locus on 16p11.2, only duplications and one inversion have been reported [20–23]. Looking at the overall clinical phenotype of our patient and the literature described ones, the only shared features seem to be autistic behaviour. The observed phenotypic variety may be caused by the dissimilarity in the nature of the chromosomal abnormalities and by the size and the content of the interval.

Large-deletion alleles on chromosome 7p22 were found in kindreds with autism but not in healthy control subjects [24]. In these regions, genes are likely to contribute to autism in the individuals with the cytogenetic abnormality but appear to lack a significant effect at the population level. More than 100 genes have been mapped in the deleted interval (http://genome.ucsc.edu/), and so it is only possible to speculate about the potential role of specific genes in autism.

According to Ensembl genome databases, there are few genes listed in the breakpoint region on 7p22.1 : NP_976327.1, which is a hypothetical gene expressed in the cerebellum, RBAK gene may contribute to transcriptional activation and cell cycle arrest and RNF216L or Q6NUR6 gene which may be an E3 ubiquitin ligase. On the basis of their functions and expression patterns, these genes can be considered as candidate genes for autism.

Interestingly, the disruption of one of these genes by the translocation may cause a decreased dosage responsible for specific tissue and developmental effects leading to autistic traits. This is in agreement with the deletions on 7p22 reported on autistic patients by Yu et al. [24].

The characterisation of the translocation breakpoints will let as to narrow the interval and to identify candidate genes causative of the observed phenotype in our patient.

In conclusion, the case report presented here (1) places further emphasis on the importance of molecular cytogenetics in the study of de novo apparently balanced translocations with abnormal phenotype and (2) confirms the possibility that genes with an important contribution to the pathogenesis of autism are located in regions of the genome for which cytogenetic abnormalities have not been reported so far.

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