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Original article

Report of a female patient with mental retardation and tall stature due to a chromosomal rearrangement disrupting the *OPHN1* gene on Xq12

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Abstract

We report on a patient with mental retardation, seizures and tall stature with advanced bone age in whom a *de novo* apparently balanced chromosomal rearrangement 46,XX,t(X;9)(q12;p13.3) was identified. Using array CGH on flow-sorted derivative chromosomes (array painting) and subsequent FISH and qPCR analysis, we mapped and sequenced both breakpoints. The Xq12 breakpoint was located within the gene coding for oligophrenin 1 (*OPHN1*) whereas the 9p13.3 breakpoint was assigned to a non-coding segment within a gene dense region. Disruption of *OPHN1* by the Xq12 breakpoint was considered the major cause of the abnormal phenotype observed in the proband.

Keywords: Translocation; *OPHN1*; Tall stature; Mental retardation

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1. Introduction

A small subset of patients with mental retardation and/or congenital abnormalities present with an apparently balanced *de novo* chromosomal rearrangement. In most patients it is assumed that the observed phenotypic anomalies are the result of submicroscopic deletions or duplications or alternatively disruption, activation or inactivation of a gene or genes located at or near the breakpoints. Until now, only a limited number of such apparently balanced *de novo* rearrangements have been investigated to the basepair level. In some instances detailed analysis has led to the identification of disease related genes [2,3,12]. Here we describe the combined application of array painting [8], FISH and real-time quantitative PCR which enabled us to map and sequence the breakpoints of a balanced reciprocal translocation t(X;9)(q12;p13.3) in a girl with mental retardation and tall stature.

2. Materials and methods

2.1. G-banding

Karyotyping was performed on short term lymphocyte cultures from peripheral blood with G-banding. Karyotypes were described according to the guidelines of the ISCN 2005.

2.2. Chromosome flow sorting

Purification of the translocated chromosomes, derivative 9 and X, was carried out using a flow cytometer (MoFlo®, DAKO) as described previously [4,8]. DNA from the flow sorted chromosomes was used as template for rolling-circle amplification (RCA) with Repli-G (Molecular Staging). The amplified DNA was subsequently used as template DNA for array painting, qPCR and sequencing [8].

2.3. Array painting

Using random prime labeling, 500 ng of amplified derivative chromosome 9 and derivative chromosome X DNA was labeled with Cy3 and Cy5 respectively (BioPrime Array CGH Genomic Labeling System, Invitrogen). Repetitive sequences were suppressed with 100 μg Cot-1 DNA (Invitrogen) and 400 μg yeast tRNA. The labeled fragments were resuspended in 60 μl hybridization buffer at 37 °C (50% formamide, 10% dextran sulphate, 0.1% Tween 20, 2× SSC, 10 mM Tris pH 7.4). In-house produced 1 Mb BAC arrays were prehybridized at 37 °C during 1 h using 50 μg Cot-1 DNA (Invitrogen) and 150 μg herring sperm DNA, resuspended in 120 μl hybridization buffer. After removal of the prehybridization mixture, DNA from both derivatives was simultaneously hybridized for 48 h at 37 °C. The slides were washed in 1× PBS/0.05% Tween 20 for 10 min at room temperature, 50% formamide/2× SSC for 30 min at 42 °C and finally 1× PBS/0.05% Tween 20 for 10 min at room temperature. After centrifuge drying, the slides were scanned using a GMS 418 Array Scanner (MWG). The scan images were processed with Imagene software (Biodiscovery) and further analyzed with our in-house developed and freely available software tool arrayCGHbase (http://medgen.ugent.be/arraycghbase/) [13]. Data points were excluded from analysis if one of the following criteria were fulfilled: signal to noise ratio <5; standard deviation of the $\log_2$ transformed ratios between triplicates >0.2; only one informative replicate.