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Short report

ARX mutation c.428–451dup (24bp) in a Brazilian family with X-linked mental retardation

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Abstract

The recently identified gene *ARX* (*Aristalles-Related Homeobox*) codifies the ARX protein, an important transcript factor that belongs to one of the three largest classes of homeoproteins, the paired (*Prd*) class. Several mutations have been identified in *ARX* gene, which is responsible for a wide spectrum of phenotypes, including syndromic as well as non syndromic forms of mental retardation. One of the mutations, the c.428-451 dup (24 bp) is the most frequent identified in the *ARX* gene. This duplication leads to an expansion of the second polyalanine tract of ARX protein. We have reported the identification of a Brazilian family segregating the c.428-451 dup (24 bp) in *ARX* gene.

Keywords: ARX; X-linked mental retardation; Dystonia; Epilepsy

1. Introduction

Although the X chromosome contains only 4% of all human genes, almost 10% of diseases with a Mendelian pattern of inheritance have been assigned to this chromosome [3]. X-linked mental retardation affects significantly more males than females, and there is now great evidence to support the idea that this sex bias is largely due to the involvement of X-linked genes that play a role in brain differentiation and function [7,10,11].

The *Aristaless Related Homeobox* (*ARX*) gene is an ortholog to the *Drosophila melanogaster aristaless homeobox* gene. This well-conserved gene maps to Xp22.13, and encom-

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passes a genomic region of 12.5 kb. It is transcribed into a single mRNA of 2.8 kb and encodes a protein product of 562 amino acids, which acts as a transcription factor expressed predominantly in the cerebral forebrain and floor plate [13]. The ARX protein belongs to the class of homeoprotein, the *paired* (*Prd*) class. This class is characterized by six invariant amino acids residues and a glutamine or serine residue at the critical position 50 (Q50/K50) of their homeodomain, and exerts primary developmental functions [1,13]. The ARX protein contains four polyalanine tracts (poly A), not seen in zebrafish and fly orthologs, and three highly conserved domains: an homeodomain, an aristaless domain (also called C peptide domain) and an octapeptide domain located near the N-terminus [5,13].

In recent years, several types of mutations were identified in *ARX* gene, including deletions/insertions, duplications, *missense* and *nonsense* mutations, responsible for a wide spectrum of phenotypes, which includes syndromic (MRXS) as well as non syndromic (MRX) forms of mental retardation [1,4–6,9,11–15].

The most frequent mutation already identified in the *ARX* gene is the c.428–451dup (24bp) at the exon 2, predicted to cause an expansion of a poly A tract of the ARX protein [13]. In this study, we report the identification of the first Brazilian family segregating the c.428–451dup mutation in the *ARX* gene.

2. Case report

The family described here lives in Rio de Janeiro, Brazil (Fig. 1). The proband (**III-2**), an 8-year-old boy (year of birth 1996), was first evaluated in 1999 for developmental delay and behavioral abnormalities. He was the second of three children of an unrelated couple, and had a family history of mental retardation in males. He was born by cesarean section for a cord around the neck, after an uncomplicated pregnancy with no intercurrence during neonatal period. The birth weight was 3.85 kg (90th centile), and the length 53 cm (90th centile). General development delay was recognized at the age of 20 months when he was walking unaided. Language delay and learning problems were also observed. The chromosomal analysis, by standard cytogenetic methods and Fragile X syndrome and FRAXE CCG analysis were performed and did not show any abnormality. The electroencephalogram (EEG) and a computed tomography (CT) scan were normal. Since then he had no significant illnesses and no seizures. He showed to be a non-cooperative boy with emo-

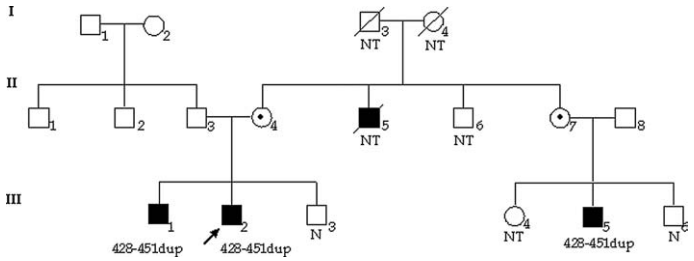

Fig. 1. Family pedigree showing the segregation of the c.428–451dup (24bp) in the *ARX* gene. Open squares represent unaffected males and open circles represent unaffected females. Solid squares represent boys with mental retardation. An arrow indicates the proband (III-2). "N" indicates *ARX* gene without duplication. "NT", is for "not available to be tested".