



Poster 21. ARX-RELATED DISORDERS: SEVERAL DISTINCT PHENOTYPES, ONE MUTATED GENE

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INTRODUCTION: Aristaless-related homeobox (*ARX*) gene is implicated in non-syndromic and syndromic intellectual disability (ID), namely X-Linked Lissencephaly with Ambiguous Genitalia, Agenesis of Corpus Callosum with Abnormal Genitalia and Early Infantile Epileptic Encephalopathy, among other phenotypes. Pathogenic mutations leading to polyalanine tract expansions in the *ARX* protein were reported in the majority of patients. Since *ARX* is one of the most frequently mutated genes causing ID with an hotspot region in exon2 and has a pleiotropic effect, it has been considered a good candidate for routine molecular screening in patients with ID, similarly to what is now recommended for Fragile X Syndrome.

OBJECTIVES: Molecular analysis of the most frequent mutations in the *ARX* gene.

MATERIAL AND METHODS: Multiplex assay for *FMR1*, *AFF2* and *ARX* genes and *ARX* sequencing (poster submitted).

RESULTS: Family 1: An eight years old boy was referred for non-syndromic ID. The pathogenic mutation c.429_452dup (*ARX*dup24) was detected in hemizyosity, causing an expansion from 12 to 20 alanines in the second polyalanine track of the *ARX* protein. Family 2: Two brothers with four and nine years old were referred for ID and macrocephaly. The disease causing mutation c.429_452dup (*ARX*dup24) was also identified in both brothers. Family 3: A twenty month old boy was referred for severe psychomotor delay, microcephaly, lissencephaly and epilepsy. The variant c.322_333dup (*ARX*dup12) was identified, resulting in an expansion from 16 to 20 alanines in the first polyalanine group of the *ARX* protein.

DISCUSSION: The screening of mutations in the *ARX* gene, followed by sequencing, enabled the diagnosis of *ARX*-Related Disorders in three families, presenting with different clinical phenotypes. The simultaneous screening of hotspot mutations in the *ARX* exon 2 gene, as well as in the *FMR1* and *AFF2* genes that cause intellectual disability, was implemented in the Unit of Molecular Genetics (Centro de Genética Médica Dr. Jacinto de Magalhães/CHP) (poster submitted). Whenever a variant is detected in this screening, sequencing is performed to precisely characterize the deletions/duplications identified. Furthermore complete sequencing of the *ARX* gene should be requested, when *ARX*-Related Disorders are suspected besides an exon 2 negative screening. The diagnosis of *ARX*-Related Disorders is crucial for genetic counselling of at risk family members.

CONCLUSIONS: Molecular analysis of the *ARX* gene should be performed in patients with non-syndromic and syndromic ID and in females with family history of ID, particularly those suggestive of X-linked inheritance pattern.