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

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INTRODUCTION: Aristless-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 (ARXdup24) was detected in hemizygosity, 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 (ARXdup24) was also identified in both brothers. Family 3: A twenty month old boy was referred for severe psychomotor delay, macrocephaly, lissencephaly and epilepsy. The variant c.322_333dup (ARXdup12) 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.