

A similar approach was used for case #2, resorting to candidate genes known to be associated with sperm immotility due to flagellar abnormalities. Variants in additional loci were also filtered by Gene Ontology. As a result, two novel variants were identified: a homozygous missense variant (p.Arg35Pro) in the *CCDC103* gene and a novel frameshift variant in the *INSL6* gene (c.262_263delCC).

The experience gathered in the study of these first two patients was important to delineate the analysis strategy for case #3, which shall be presented in this work. We propose a new bioinformatic pipeline for the analysis of AR diseases using WES, combining variant filtering and autozygosity mapping.

Concluding remarks: Considering the present state of the art, WES should be seen as a screening method. There are technical and analytical limitations to be properly addressed in WES before incorporating it in routine diagnostics. Our experience, in line with recent scientific reports, suggests that WES is presently one of the most efficient and cost-effective approaches to study highly heterogeneous rare diseases.

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PHENOTYPIC SPECTRUM OF *DCX* PATHOGENIC MUTATIONS IN FEMALES: FROM CHILDHOOD TO ADULTHOOD CLINICAL ONSET

Maria João Sá^{1,2}, Rui Chorão³, Manuela Santos³, Ana Maria Fortuna^{1,2}, Gabriela Soares¹

¹ Unit of Medical Genetics, Centro Genética Médica Doutor Jacinto Magalhães, Centro Hospitalar do Porto - EPE, Porto, Portugal

² Multidisciplinary Unit for Biomedical Research, UMIB, Porto, Portugal;

³ Department of Neuropediatrics, Hospital de Santo António/Centro Hospitalar do Porto - EPE, Porto, Portugal
m.joao.sa@chporto.min-saude.pt

Introduction: *DCX*-related disorders (MIM#300067) are caused by pathogenic mutations in the *DCX* gene (MIM*300121; Xq23) that result in abnormal neuronal migration patterns, including isolated lissencephaly sequence (ILS) and subcortical band heterotopia (SBH; also called double cortex). Often occurring in males, ILS causes intellectual disability (ID) and childhood-onset epilepsy. More common in females, SBH is associated with a broad spectrum of clinical features, from ID and epilepsy to normal intelligence without epilepsy. We report two families that illustrate the phenotypic spectrum of *DCX* pathogenic mutations in females, from childhood to adulthood onset.

Patients and methods: Family 1: A 3 years old boy, born to non-consanguineous parents, presented with global developmental delay, seizures and microcephaly. Brain MRI diagnosed fronto-parietal classic lissencephaly. Sequence analysis of *DCX* detected a novel likely pathogenic variant, c.806G>T, p.(Gly269Val), in hemizyosity. Segregation analysis confirmed that his mother, who has mild ID and a frontal simplified gyration pattern shown by brain MRI, carries this variant in heterozygosity. Family 2: A 15 years-old girl, born to non-consanguineous parents, had epilepsy since 4 years old and global developmental delay. Brain MRI showed SBH and the previously reported pathogenic variant c.1150C>T, p.(Arg384*) was identified in *DCX* gene, in heterozygosity. Her mother, who carried the same mutation, had epilepsy with onset at 19 years old, an unremarkable brain MRI and normal intelligence.

Discussion: Pathogenic *DCX* mutations are identified in approximately 40% of males with classic lissencephaly (more severe anteriorly than posteriorly), as well as in 85% of patients with SBH. Given the well-known genotype-phenotype correlation in *DCX*-related disorders, the decision of testing this gene was made based on the clinical and cerebral imaging features of the probands.

A novel likely pathogenic variant was identified in *DCX*, increasing the genotypic spectrum of mutations in this gene. *DCX* mutations were also detected in the probands' mothers, who had previously non-investigated mild ID (family 1) and adult-onset epilepsy (family 2).

DCX-related disorders may not be clinically recognizable in females due to its clinical heterogeneity. Consequently,

molecular testing of *DCX* is warranted in the mothers of affected children, allowing genetic counselling to at-risk family members, including prenatal diagnosis and preimplantation genetic diagnosis. Massive parallel sequencing, either whole exome or gene panels, of females with ID with or without epilepsy will likely increase detection of mutations in the *DCX* gene.

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A PORTUGUESE FAMILY WITH CADASIL DIAGNOSIS WITH ANTICIPATION AGE OF ONSET OBSERVED

Maria Lopes-de-Almeida¹, Lina Ramos¹, Gustavo Cordeiro², Rosário Almeida³, Joaquim Sá¹, Jorge M Saraiva^{2,4}

¹ Medical Genetics Unit, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal;

² Neurology Unit, Hospital Universitário de Coimbra, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal;

³ Center of Neuroscience and Cell Biology, Faculty of Medicine, University of Coimbra, Portugal;

⁴ University Clinic of Pediatrics, Faculty of Medicine, University of Coimbra, Portugal

marialopesdealmeida@chc.min-saude.pt

Introduction: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a rare hereditary disease characterized by recurrent transient ischemic attacks, strokes, and vascular dementia.

Since it is a dominant disease, heterozygous and homozygous patients are expected to be clinically indistinguishable. Nevertheless, some homozygous patients with CADASIL have been reported and in some cases with a severe phenotype.

Case report: We would like to report a Portuguese family with inbreeding with diagnosis of CADASIL. It has been found the p.Arg558Cys mutation in *NOTCH3* gene in six members of this family studied, two of them in homozygosity. One of the homozygous case present a more severe phenotype compared with his relatives with an age of onset at 10 years old. According to this finding, we wonder if the homozygosity can justify this early age of onset case or its severity.

Discussion: Differences in clinical profile between homozygous and heterozygous of this family members and between other CADASIL families with homozygosity described should be discuss in order to understand if the homozygosity state increases the pathologic consequences of the mutation providing a more severe and early phenotype.