Classification of the dup 15q13.3 CNV: A National data collection


1Serviço de Genética Médica, Departamento de Pediatria, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte; 2Laboratório de Citogenética e Genómica, Faculdade de Medicina da Universidade de Coimbra; 3Departamento de Genética, Faculdade de Medicina da Universidade do Porto; 4CGC Genetics/Centro de Genética Clínica; 5Serviço de Pediatria, Centro Hospitalar do Porto; 6Genética Médica e Diagnóstico Pré-Natal Prof. Doutor Sérgio Castedo; 7Serviço de Genética Médica, Joaquim Chaves Saúde; 8Departamento de Genética Humana, Instituto Nacional de Saúde Dr. Ricardo Jorge; 9Escola de Ciências da Saúde, Universidade do Minho

Introduction: The proximal region 15q11q14 is one of the most unstable regions in the human genome, with six recognizable break points (BP1-BP6). In 15q13.3 there is a recurrent small CNV (BP4-BP5) consisting of a 350-680 Kb duplication, encompassing the CHRNA7 gene, which encodes the alpha 7 subunit of the neuronal nicotinic acetylcholine receptor.

Although microdeletions of CHRNA7 are known to cause intellectual disability and neuropsychiatric phenotypes with high penetrance, the patogenicity of CHRNA7 duplications remains unclear. Microduplication 15q13.3 seems to be associated with a phenotypic spectrum of cognitive impairment and neuropsychiatric/neurobehavioral disorders. However, the penetrance of this CNV is considered incomplete since it is present in clinically unaffected individuals in the general population and it is frequently inherited from apparently clinically normal parents. Nonetheless, some pedigree studies have found a history of neuropsychiatric problems among carrier family members.

This study aimed at re-evaluating the dup 15q13.3 CNV in national laboratories.

Materials and Methods: Our study collected data on 15q13.3 microduplications in eight Portuguese genetics laboratories, among subjects referred for microarray.

Results: Here we present a total of seventeen cases with dup 15q13.3. The subjects had somewhat variable phenotypes, with a bias towards developmental delay and autism spectrum disorders. Inheritance was established for eight of the subjects, and the majority originated from the father. We had no access to clinical data on carrier parents. No de novo CNV was found. All laboratories involved classified this variant as of uncertain significance.

Discussion/Conclusion: To better determine whether this CNV is benign or pathogenic, careful characterization of patient and control cohorts must be performed, including detailed patient phenotyping, inheritance, clinical evaluation of carrier parents, prevalence in controls, as well as genetic functional studies. We strongly support the creation of a national database for uncertain CNVs in order to clarify the relevance of these recurrent findings, allowing a definitive classification in either pathogenic or benign.