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

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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.

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