

eP1537**Investigation into C9ORF72 hexanucleotide repeats in patients with Machado-Joseph Disease and a possible correlation with age of onset: preliminary analysis**

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Introduction. Machado-Joseph disease (MJD) is a neurodegenerative disorder with an autosomal dominant hereditary pattern. MJD is caused by an expansion of a CAG repeat track in the ATXN3 gene. Previous studies show that age of onset (AO) of the disease is inversely correlated with the number of CAG repeats in the expanded allele. However, only between 40 to 68% of AO variation can be explained by this factor, leaving at least 30% of variation entirely unaccounted for. Taking into consideration scientific support for a shared molecular mechanism for all inherited genetic neurodegenerative diseases, the key to describing this variation could lie in the molecular biology of other, related diseases. Recently, a pathway of protein degradation via Gp78 has been identified as a molecular link between MJD and amyotrophic lateral sclerosis (ALS). In 2011, a hexanucleotide repeat expansion in C9orf72 was identified as the etiology in a significant portion of ALS patients as well as patients of frontotemporal dementia (FTD) and those affected by comorbid ALS-FTD. **Objective.** Investigate the occurrence and modifying effects of the C9orf72 hexanucleotide expansion in MJD patients. **Methods.** A total of 80 MJD patients with a molecular diagnosis and 100 controls with no history of ataxia were recruited at the Hospital de Clínicas de Porto Alegre and will be included in the study. At first, a reliable protocol for genotyping alleles within normal range of C9Orf72 was introduced using conventional PCR with a fluorescent primer in order to select candidate expansion carriers. Expanded alleles will be genotyped via repeat-primed PCR (RP-PCR), a protocol designed to identify very large expansions. MJD patients will be divided into two groups based on AO (early- and late-onset) for the purposes of analysis. **Results.** Up to date, 34 samples have been analyzed (23 MJD and 11 controls). Two distinct alleles were observed in 20 samples (12 MJD and 8 controls). Interestingly, 17 samples presented only 1 hexanucleotide expansion, a genotype either absent or rare in previously studied populations. **Conclusion.** Protocol for a complete analysis was fully established and analyses will continue until we reach our proposed cohort size. However, data generated is still too preliminary to draw any further conclusions. **Keywords:** Machado-Joseph Disease, modifying factors, C9ORF72