ANALYSIS OF VARIATIONS IN THE PROMOTER REGION OF DNAJB6 GENE IN MACHADO-JOSEPH DISEASE PATIENTS

Musskopf, M.K. 1,2; Mattos, E.P. 1,2,3; Furtado, G.V. 1,2,3; Saute, J.A.S. 1,2; Jardim, L.B. 1,2,3,4; Saraiva-Pereira, M.L. 1,2,3,5

1Laboratório de Identificação Genética – Centro de Pesquisa Experimental – HCPA; 2Serviço de Genética Médica – HCPA; 3PPG em Genética e Biologia Molecular – UFRGS; 4Departamento de Medicina Interna – UFRGS; 5Depto. de Bioquímica – UFRGS, Porto Alegre, RS, Brazil.

Machado-Joseph disease (MJD/SCA3) is a neurogenetic disease characterized by an expansion of the CAG trinucleotide in the ATXN3 gene. MJD/SCA3 starts typically in the adult life, with mean age at onset (AO) of symptoms of 30-50 years and shows an inverse correlation with AO. However, other factors - genetic and/or environmental - seem to influence AO, since patients with the same expansion length may present discordant AOs. Several studies have demonstrated that DNAJB6 could be a potential modifier of AO, as part of protein quality control system, and could modulate intracellular aggregates. We have recently seen alteration in DNAJB6 expression levels in MJD/SCA3 patients. Thereby, the objective of this study is to search for polymorphic variants and/or rare mutations in the promoter region of DNAJB6 gene that may modulate AO in MJD/SCA3 patients. DNA samples from 45 patients that show extreme AO (outliers, i.e. early or late AO). In addition, 20 samples from healthy controls were also tested to determine allelic and genotypic frequencies of these variants in the normal population. A fragment of 441bp (ranging from -942 to -502) was amplified by PCR, followed by DNA Sanger sequencing using the BigDye® kit. Amplified fragments were resolved by capillary electrophoresis and results were analyzed by SeqScape software v2.5. Statistical analyses were performed using SPSS software. Nine out of eleven markers were homoallelic, and allelic and genotypic frequencies of rs3807439 and rs3807440 were established in patients (early and late AO) and compared to controls as well as to worldwide frequencies. No statistical differences were observed. Results presented here analyzed part of the whole promoter region. Analysis of the remaining region will be carried out to evaluate whether other variants located somewhere else in the promoter can be associated to AO and be responsible for different expression of DNAJB6 in MJD/SCA3 patients.

Key words: MJD/SCA3, DNAJB6, polymorphic variants

Financial Support: CNPq, FIPE-HCPA.