Does DNA Methylation in Promoter Region of ATXN3 Gene Modify Age of Onset in SCA3 Patients?

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Spinocerebellar ataxia type 3 (SCA3) is a neurodegenerative disease caused by expansion of a polyglutamine domain in the protein ataxin-3. The length of CAG is inversely correlated with age of onset of disease. However, a broad range of age at onset is typically observed in individuals with the same CAG repeats. In this study, we investigate whether ataxin-3 protein levels can be influenced by *de novo* DNA methylation, which would specifically target the allele with the expanded CAG repeat leading to transcriptional silencing. We have designed a methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) for a quantitative analysis of methylation status of 6 CpG sites located within the promoter region of ATXN3 gene. We have then applied this MS-MLPA to 123 SCA3 Brazilian patients and to 35 controls individuals. The age of onset varied from 9 to 57 years (mean 35.01 ± 11.32 SD). No differences were found in methylation degree between SCA3 patients and controls. However, when we compared methylation degree between SCA3 individuals with age of onset up to 35 years old and SCA3 individuals with age of onset older than 35 years, we found differences for one CpG island (p=0.007). SCA3 individuals with older age of onset had the larger methylation degree. Epigenetic control in this CpG-island may contribute to age of onset variation in SCA3 patients.

Keywords: SCA3, DNA methylation, CAG repeat, age of onset

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